Use of an aromatase inhibitor compound of formula (I) for therapeutic ends and compounds of the formula (I) as such

FIELD OF THE INVENTION

The present invention relates to new compounds inhibitory to aromatase and their utilization in the medical field, and more specifically in the prevention and treatment of cancer, particularly breast cancer, or of psoriasis.

PRIOR ART

Certain derivatives of the benzazolinones and particularly of benzoxazolinone, have already been described for their gonadotrope, antiproliferative and immunomodulating properties (BERGER et al.1981 ; BUTTERSTEIN, et al. 1988 ; SCHADLER et al. 1988).

In the course of the last ten years, the azole class of compounds (imidazoles and triazoles) has shown activity inhibitory to aromatase that has led to their use in the treatment of certain breast cancers (KUIJPERS et al. 1998 ; SCHADLER et al. 2001 ; BRODIE et al. 2002).

It has been shown that, in mammals, and in particular in humans, oestrogens are synthesised from androgens by enzyme catalysis with aromatase. It is readily acknowledged that inhibition of aromatase is useful in the prevention or the treatment of disorders and pathologies associated with oestrogens in mammals, such as breast cancer. The other diseases associated with oestrogens which can be treated with a compound inhibitory to aromatase include endometriosis, cancer of the neck of the uterus, cancer of the ovaries, polycystic ovarian syndrome. It is also considered that an aromatase inhibitor compound is useful for birth control. More particularly, in the case of breast cancer, it is said that an aromatase inhibitor compound can be advantageously used, as a replacement for typical surgical treatment such as ovariectomy or adrenalectomy.

It is also known that an aromatase inhibitor compound is useful in the prevention or treatment of cancer of the prostate.

The benefit has also been shown of using an aromatase inhibitor compound for the treatment of psoriasis.

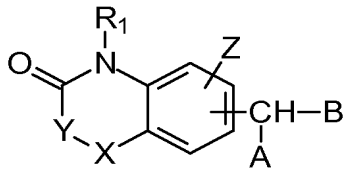
Notably olefinic compounds inhibitory to aromatase comprising one or several heterocycles are described in the European patent application n° EP-299 683. Other aromatase inhibitor compounds, such as the compound designated "TAN-931", have been described in the European patent application n° EP-342 665. Also the aromatase inhibitor compounds diarylalkyl heterocyclics such as those described in the PCT application n° WO 94/13645 or in the PCT application n° WO 02/087571 are known. Equally the heterocyclic derivatives of aralkyl aromatase inhibitors, as described in the European patent application n° EP-296 749 are known. Also described are the aromatase inhibitor compounds composed of imidazolyl or triazolyl derivatives of pyrimidine or of dihydropyridine substituted by a phenyl, as in the applications for European patent n° EP-755 931 and n° EP-533 504, or again as in the PCT application n° WO 90/06923. Condensed tricyclic aromatase inhibitors have also been described in the European patent application n° EP-360 324.

Nevertheless, there exists a need, in the state of the art, for new compounds inhibitory to aromatase, useful in therapy, which offer good properties for inhibition of this enzyme, and which are without toxicity, both *in vitro* and *in vivo*.

DETAILED DESCRIPTION OF THE INVENTION

The present invention concerns the preparation of new azole derivatives of various benzazolinones, (benzoxazolinone, benzothiazolinone, benzoselenazolinone, benzoxazinone, benzothiazinone and indolinone), which possess aromatase inhibitory properties and remarkable anti-cancer and anti-psoriasis properties.

The object of the invention is the utilization of a compound of the formula (I) below:



(I)

wherein:

. **R_1** represents an atom of hydrogen or a linear or branched alkyl (C_1-C_6), alkenyl (alkene) (C_1-C_6), or alkynyl (alkyne) (C_1-C_6) radical,

. **X** represents an atom of oxygen, sulphur or selenium;

. **Y** represents a single bond or a CH_2 group, possibly substituted by one or two lower alkyl groups.

. **Z** represents an atom of hydrogen or halogen, or a hydroxy or a linear or branched alkoxy group.

. **A** represents an imidazole, triazole or tetrazole nucleus,

. **B** represents a group selected from the groups phenyl, naphthyl, biphenyl or also a monocyclic or bicyclic heteroaryl group having 5 to 10 bonds and containing 1 to 3 heteroatoms.

the groups phenyl, naphthyl, biphenyl and heteroaryl being non-substituted or substituted with 1 to 3 groups selected from alkyl (C_1-C_6), alkoxy (C_1-C_6), carboxy, formyl, amino, amido, ester, nitro, cyano, trifluoromethyl, or atoms of halogen,

as well as enantiomers and diastereomers of compounds of formula (I),

as well as the salts from the addition to an acid or to a pharmaceutically acceptable base of compounds of the formula (I),

for preparation of a pharmaceutical formulation intended for treatment of cancer or psoriasis.

The term “heteroaryl” means, according to the invention, all mono- or bi-cyclic groups comprising 5 to 10 bonds and 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. In the meaning of the invention, heteroaryl groups containing 5, 6, 7, 8, 9, or 10 bonds are included. The heteroaryl groups comprising 1, 2 or 3 heteroatoms selected from among oxygen, nitrogen and sulphur are included.

The groups aryl and heteroaryl B of a compound of formula (I) such as defined herein can be substituted with 1, 2 or 3 groups selected from among alkyl (C_1-C_6), alkoxy (C_1-C_6), carboxy, formyl, amino, amido, ester, nitro, cyano, trifluoromethyl, or atoms of halogen. Therefore, in the meaning of the invention, the groups C_1-, C_2-, C_3-, C_4-, C_5-, and C_6- alkyl, as well as the groups C_1-, C_2-, C_3-, C_4-, C_5-, and C_6- alkoxy are included.

All salts from the addition of a compound of formula (I) to a pharmaceutically acceptable acid are included in the invention. Among the acids pharmaceutically acceptable, are cited preferably, but not limitatively, the hydrochloric, hydrobromic, sulphuric, acetic, trifluoroacetic, lactic, succinic, fumaric, citric, oxalic or methane sulphonic acids.

All salts from the addition of a compound of formula (I) to a pharmaceutically acceptable base are included in the invention. Among the pharmaceutically acceptable bases, are cited for preference, but not limitatively, sodium hydroxide, potassium hydroxide or triethylamine.

It has been shown according to the invention that compounds of the formula (I) defined herein are highly innocuous, *in vitro* as well as *in vivo*. Thus, it is shown that compounds of the formula (I) are not cytotoxic *in vitro*. It has also been shown that a compound of formula (I) presents no danger, even at a high dose, when it is administered to an individual.

It has also been shown according to the invention that compounds of formula (I) are good aromatase inhibitors. Certain compounds of the formula (I) present an inhibitory power IC_{50} of the order of 1 nM.

Equally it has been shown that compounds of the formula (I) are active in vivo, as illustrated by their capacity to inhibit and, in some cases, block, the uterine hypertrophy induced by androstenedione.

In general, the preferred compounds of formula (I) according to the invention are the compounds n° 1 to 51, described in examples 1 to 51, the structure of which is described in detail in Table IV.

The first family of preferred compounds of formula (I) according to the invention is comprised of compounds for which the group B is selected from among:

- unsubstituted benzene or benzene substituted in the meta or para position by a group selected from among the groups cyano or nitro, or by a chlorine atom;
- a heterocyclic pyridine.

A second family of preferred compounds of formula (I) according to the invention is comprised of compounds for which the group R1 represents a hydrogen atom or a methyl group.

A third family of preferred compounds of formula (I) according to the invention is comprised of compounds for which the group Z represents a hydrogen atom or a methoxy group.

A fourth family of preferred compounds of formula (I) according to the invention is comprised of compounds for which the group A represents a 1,3-imidazolyl or 1,2,4-triazolyl group.

A fifth family of preferred compounds of formula (I) according to the invention is comprised of compounds for which, simultaneously:

(i) group B is selected from among:

- unsubstituted benzene or benzene substituted in the meta or para position by a group selected from among the groups cyano or nitro, or by a chlorine atom;
- a heterocyclic pyridine;

(ii) group R1 represents a hydrogen atom or methyl group;

(iii) group Z represents a hydrogen atom or methoxy group; and

(iv) group A represents a 1,3-imidazolyl or 1,2,4-triazolyl group.

Another object of the invention is an aromatase inhibitor compound, such as defined herein, for use as an active ingredient of a medicine.

The invention equally concerns, as a new compound, any of the compounds of formula (I) as described in the present description.

In their role for therapy, the compounds of formula (I) are particularly useful when they are used in manufacturing a pharmaceutical formulation intended for the prevention or the treatment of disorders and pathologies associated with oestrogens in mammals, such as breast cancer, endometriosis, cancer of the neck of the uterus, ovarian cancer, prostate cancer or polycystic ovarian syndrome.

A compound of formula (I) is equally advantageously used to manufacture a pharmaceutical formulation intended for treatment of psoriasis.

The present invention also has for an object a pharmaceutical formulation characterized in that it comprises at least one compound of general formula (**I**) described herein, in association with at least one excipient selected from among the group consisting of pharmaceutically acceptable excipients.

To make a pharmaceutical formulation according to the invention, those skilled in the art could advantageously refer to the last edition of the European Pharmacopoeia or the United States Pharmacopoeia (USP).

Those skilled in the art could particularly advantageously refer to the 4th edition "2002" of the European Pharmacopoeia, or edition USP 25-NF20 of the American Pharmacopoeia (U.S. Pharmacopoeia).

Advantageously, a pharmaceutical formulation such as defined is adapted to daily administration, preferably by the oral route or topically, of a quantity of the compound of formula (I) ranging from 1 μg to 10 mg and preferably from 0.5 mg to 10 mg.

Advantageously, a pharmaceutical formulation such as defined herein is adapted for daily systemic administration of a quantity of the compound of formula (I) ranging from 0.5 mg to 10 mg.

When the formulation according to the invention comprises at least one pharmaceutically acceptable excipient, this is in particular an excipient appropriate for administration of the formulation by the topical route and/or an excipient appropriate for administration of the formulation by the oral route.

Administration by the systemic route is preferred for a pharmaceutical formulation comprising a compound of formula (I), for example by the oral route, for the prevention or treatment of a cancer.

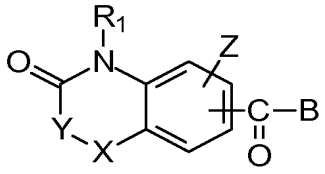
Administration by the topical route is preferred for a pharmaceutical formulation comprising a compound of formula (I) for the treatment of psoriasis.

The invention also relates to a method for treating cancer in a patient, preferentially a cancer associated with oestrogens, said method comprising a step in the course of which the patient is administered a therapeutically effective quantity of a compound of formula (I) or a pharmaceutical formulation containing a compound of formula (I).

The invention also relates to a method for preventing cancer in a patient, preferentially a cancer associated with oestrogens, said method comprising a step in the course of which the patient is administered a therapeutically effective quantity of a compound of formula (I) or a pharmaceutical formulation containing a compound of formula (I).

The invention also relates to a method for treating psoriasis in a patient said method comprising a step in the course of which the patient is administered a therapeutically effective quantity of a compound of formula (I) or a pharmaceutical formulation containing a compound of formula (I).

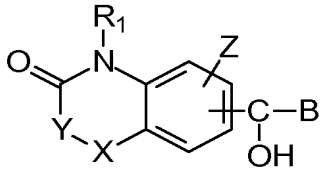
The present invention equally relates to the process for obtaining compounds of formula (I) characterized in that the starting product used is a compound of formula (II).



(II)

wherein R_1, X, Y, Z and B have the same meaning as in formula (I) obtained according to one of the protocols described by BONTE et al. 1974 ; AICHAOUI et al. (1990, 1991 and 1992), MOUSSAVI et al. (1989), SASTRY et al. (1988), and YOUS et al. (1994)

which is reduced to obtain a compound of formula (III).



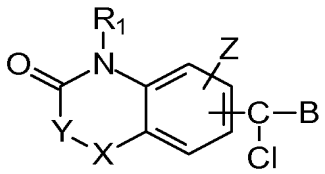
(III)

wherein R_1, X, Y, Z and B have the same meaning as in formula (I)

which is subsequently:

-either treated with carbonyldiimidazole in order to obtain a compound of formula (I).

- or treated with thionyl chloride to lead intermediately to a non-isolated compound of formula (IV).



(IV)

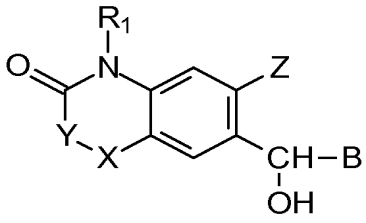
which is reacted with an azole derivative: imidazole, triazole or tetrazole, in order to obtain compounds of formula (I)

The preparatory separations of enantiomers of certain compounds selected from among the most active were achieved with the help of stationary phase chiral polysaccharide columns (cellulose or amylose) using a non-polar mobile phase.

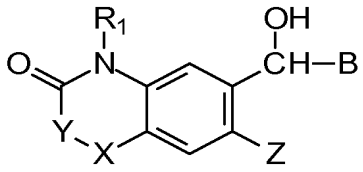
The optical purity of each enantiomer isolated was then measured with the help of analytic columns of the same chiral stationary phase as those having performed the preparative separation and in the same operating conditions.

The materials first used in the previously described procedure are either commercial, or easily available to those skilled in the art following the literature and the preparation examples given hereunder.

For example, it is possible to prepare the compounds of formula (IIIa) or (IIIb)



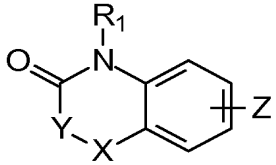
(IIIa)



(IIIb)

wherein R_1, X, Y, Z and B have the same meaning as in formula (I)

by reaction of a compound of formula (V)



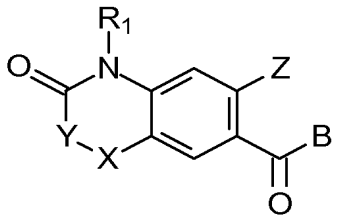
(V)

wherein R_1, X, Y, Z and B have the same meaning as in formula (I)

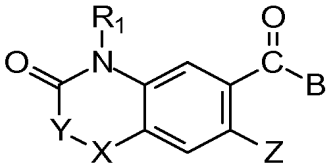
. either with a chloride or an acid anhydride of formula B-COCl or $(B\text{-}CO)_2O$, in the presence of aluminium trichloride and of dimethylformamide

. or with an acid of formula B-COOH, in the presence of polyphosphoric acid

to obtain a compound of formula (IIa) or (IIb)



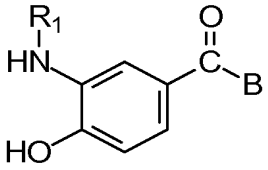
(IIa)



(IIb)

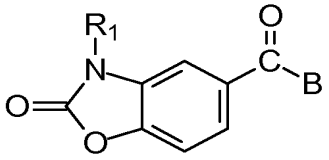
wherein R_1, X, Y, Z and B have the same meaning as in formula (I) which is reduced by sodium borohydride to obtain a compound of formula (IIIa) or (IIIb)

A further example of preparation of compounds of formula (I) consists in using the 4-acyl 2-aminophenols of formula (VI)



(VI)

wherein R1, X, Y, Z and B have the same meaning as in formula (I) to obtain by heterocyclisation according to a protocol described by AICHAOUI et al. (1990) 5-acyl benzoxazolinones of formula (IIc)



(IIc)

which are then subjected to the same reaction sequence as before.

Other routes of synthesis of compounds of formula (I) according to the invention are described in the examples and illustrated in figures 4 and 5.

The present invention is further illustrated by the following figures and examples.

DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates a first synthesis diagram of a compound of formula (I) according to the invention.

Figure 2 illustrates a second synthesis diagram of a compound of formula (I) according to the invention.

Figure 3 illustrates a third synthesis diagram of a compound of formula (I) according to the invention.

Figure 4 illustrates a synthesis diagram of a compound of formula (I) according to the invention, of the 5-benzothiazolinone type.

Figure 5 illustrates a synthesis diagram of a compound of formula (I) according to the invention, of the 6-benzoselenazolinone type.

EXAMPLES

The following embodiments illustrate the invention and do not limit it in any way. The following preparations lead to synthesis intermediates used in the invention preparation.

The products described in the "preparations" are not part of the invention. However their description facilitates the making of the compounds of formula (I) of the invention.

A. General method of synthesis of compounds of formula (I) of the invention.

A.1. Preparation 1: 6-Acyl benzazinones and 7-acyl-benzothiazinone (Table I-A)

The 6-acyl benzoxazolinones, benzothiazolinones, benzoxazinones, indolinones and 7-acyl-benzothiazinones and benzoselenazolinones are obtained from the corresponding benzazolinones according to two known procedures and using either chloride or acid anhydride in the presence of aluminium trichloride in methylformamide (Method B), or the organic acid itself in the presence of polyphosphoric acid (Method A) (AICHAOUI et al, 1992; BONTE et al, 1974; SASTRY et al, 1988; YOUS et al, 1994).

A.2. Preparation 2: 5-Acyl benzoxazolinones (Table II).

The 5-acyl benzoxazolinones are prepared from 4-acyl-2-aminophenols according to the procedure described by AICHOUI et al, (1990).

A.3. Preparation 3: 7-Acyl benzoxazinones (Table II)

The 7-acyl benzoxazinones are prepared from 5-acyl-2-aminophenols according to the procedure described by MOUSSAVI et al. (1989).

A.4. Preparation 4: Hydroxyarylmethyl benzazinones (Table III-A)

Dissolve acyl benzazinone in methanol (R_1 = alkyl, method A) or in an aqueous solution of sodium hydroxide (R_1 = H, method B). Slowly add with stirring 2 equivalents of sodium borohydride then stir at ambient temperature for three hours and acidify with 6M hydrochloric acid. Spin out the precipitate, wash with water, dry and recrystallise in an appropriate solvent.

B. Examples of synthesis of compounds of formula (I)

Example 1: 6-[(4-Cyanophenyl)(1*H*-imidazol-1-yl)methyl]-1,3-benzoxazol-2(3*H*)-one. In 30 ml of acetonitrile, 5 mole of 6-[1-hydroxy-1-(4-cyanophenyl)methyl]-1,3-benzoxazol-2(3*H*)-one and 5 mmole of *N,N'*-carbonyldiimidazole are refluxed for 24 hours. The solvent is then evaporated under vacuum. The residue is triturated with 100 ml of water then acidified with 6M hydrochloric acid and extracted with diethyl ether. The aqueous phase is alkalised with a saturated solution of sodium carbonate then extracted twice with 100 ml of ethyl acetate. The organic phase is washed with water, dried on magnesium sulphate and vaporised. The residue obtained is purified by column chromatography. The fractions containing the product are vaporised and the residue obtained is triturated with petroleum ether before drying. F°C: 122-126 °C.

Examples 2 to 19: By proceeding as in example 1, but replacing the 6-[1-hydroxy-1-(4-cyanophenyl)methyl]-1,3-benzoxazol-2(3*H*)-one by the appropriate hydroxyarylmethyl benzazinone, the products in examples 2 to 19 (table IV) are obtained.

Example 20: 6-[(4-Cyanophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-3-methyl-1,3-benzothiazol-2(3*H*)-one. Thionyl chloride (15 mmol) is added to a solution of 1*H*-1,2,4-triazole (60 mmol) in acetonitrile (30 ml). The reaction mixture is stirred for 1 h at ambient temperature before being filtered. The solution obtained is added drop by drop to a solution of 6-[1-hydroxy-1-(4-cyanophenyl)methyl]-1,3-benzoxazol-2(3*H*)-one (4 mmol) in acetonitrile (10 ml). After 5 h of stirring at ambient temperature the solvent is evaporated under vacuum. The residue obtained is triturated with 100 ml of water then acidified with 6M hydrochloric acid and extracted with diethyl ether. The aqueous phase is alkalised with a saturated solution of sodium carbonate then extracted twice with 100 ml of ethyl acetate. The organic phase is washed with water, dried on magnesium sulphate and vaporised. The residue obtained is purified by column chromatography. The fractions containing the product are vaporised and the residue obtained is triturated with petroleum ether before drying. F°C 127-130 °C.

Examples 21 to 24: By proceeding as in example 20, but replacing the 6-[1-hydroxy-1-(4-cyanophenyl)methyl]-1,3-benzothiazol-2(3H)-one by an appropriate hydroxyarylmethyl benzazinone, the products in examples **21** to **24** (table IV) are obtained.

Examples 25 to 43

Proceeding as in the preceding examples, one obtains similarly:

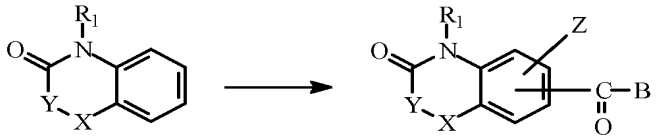
- 6-[1*H*-Imidazol-1-yl(phenyl)methyl]-1,3-benzoxazol-2(3*H*)-one (**25**). F °C 193-195 °C
- 6-[1*H*-Imidazol-1-yl(phenyl)methyl]-3-methyl-1,3-benzoxazol-2(3*H*)-one (**26**). F °C73-74 °C
- 6-[(4-Chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-1,3-benzoxazol-2(3*H*)-one (**27**).
F°C 76-78 °C.
- 3-Methyl-6-[phenyl(4*H*-1,3,4-triazol-4-yl)methyl]-1,3-benzoxazol-2(3*H*)-one (**28**).
F°C 225-226 °C.

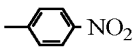
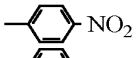
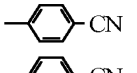
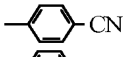
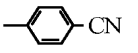
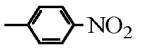
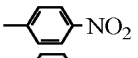
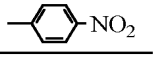
- 3-Methyl-6-[phenyl(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-benzoxazol-2(3*H*)-one (**29**).
F°C 76-78 °C.
- 5-[1*H*-Imidazol-1-yl(phenyl)methyl]-1,3-benzoxazol-2(3*H*)-one (**30**). F °C 108-111 °C
- 3-Methyl-5-[1*H*-imidazol-1-yl-(phenyl)methyl]-1,3-benzoxazol-2(3*H*)-one (**31**). F °C 133-135°C
- 3-Methyl-5-[1*H*-1,2,4-triazol-1-yl(phenyl)methyl]-1,3-benzoxazol-2(3*H*)-one (**32**). F °C 135-138°C
- 5-[(4-Chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-3-methyl-1,3-benzoxazol-2(3*H*)-one (**33**).
F°C 70-74°C
- 5-[(4-Cyanophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-6-methoxy-1,3-benzoxazol-2(3*H*)-one (**34**).
F°C 125-130°C
- 6-[1*H*-Imidazol-1-yl(phenyl)methyl]-1,3-benzothiazol-2(3*H*)-one (**35**).F °C 55-60 °C
- 6-[1*H*-Imidazol-1-yl(phenyl)methyl]-3-methyl-1,3-benzothiazol-2(3*H*)-one (**36**).
F°C 65-68 °C
- 3-Methyl-6-[phenyl(1H-1,2,4-triazol-1-yl)methyl]-1,3-benzothiazol-2(3*H*)-one (**37**).
F°C 150-154 °C
- 6-[(4-Chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-benzothiazol-2(3*H*)-one (**38**).
F°C 106-112 °C
- 6-[1*H*-Imidazol-1-yl(4-nitrophenyl)methyl]-1,3-benzothiazol-2(3*H*)-one (**39**). F °C 238-241
- 4-Methyl-7-[1*H*-imidazol-1-yl(phenyl)methyl]-1,4-benzoxazin-3(4*H*)-one (**40**).
F °C 66-68 °C
- 4-Methyl-7-[phenyl(1*H*-1,2,4-triazol-1-yl)methyl]-1,4-benzoxazin-3(4*H*)-one (**41**).
F °C 160-164 °C

- 4-Methyl-6-[phenyl(1*H*-1,2,4-triazol-1-yl)methyl]-1,4-benzoxazin-3(4*H*)-one (**42**).
F °C 140-150 °C

- 7-[1*H*-Imidazol-1-yl(phenyl)methyl]-1,4-benzothiazin-3(4*H*)-one (**43**). F °C 187-189 °C

PREPARATION OF COMPOUNDS OF EXAMPLES 44 to 49 (Tables I-B, III-B, IV)



Ref	R_1	X	Y	Z	Isomer	B
1	H	S	–	H	6	
2	CH_2CH_3	S	–	H	6	
3	H	Se	–	H	6	
4	CH_3	Se	–	H	6	
5	CH_2CH_3	Se	–	H	6	
6	H	Se	–	H	6	
7	CH_3	Se	–	H	6	
8	CH_2CH_3	Se	–	H	6	

6-(4-Nitrobenzoyl)-1,3-benzothiazol-2(3*H*)-one (1; Table I-B). In a 100 ml flask containing 35.0 g (265 mmol) aluminium chloride, add drop by drop and with magnetic stirring 5.9 ml of dimethylformamide (76 mmol). Continue stirring for 25 minutes, slowly add 5.0 g (33 mmol) of 2(3*H*)-benzothiazolone and heat to 90°C. Add drop by drop 7.36 g of 4-nitrobenzoyl chloride (40 mmol) and continue to stir at 100-110 °C for 4 hours. Slowly pour the reaction mixture onto ice while stirring vigorously. Add 15 ml of 37% hydrochloric acid and then stir for 15 minutes. Spin out the precipitate then wash with water until the wash water is neutral. Dry

the product obtained and recrystallise it in dioxane (5.85 g, 59%). Rf = 0.39 (EtOAc/Cyclohexane = 4/6): mp 260-265 °C; ir γ NH 3369 cm^{-1}, CO 1682 cm^{-1}, 1651 cm^{-1}, NO_2 1521 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-d_6) δ 7.26 (d, 1H, H_4, J_{4-5} = 7.8 Hz), 7.72-7.74 (m, 1H, H_5), 7.92 (d, 2H, $H_{3'}$, $H_{5'}$, J = 9.0 Hz), 8.09 (s, 1H, H_7), 8.36 (d, 2H, $H_{2'}$, $H_{6'}$, J = 9.0 Hz), 12.3 (br s, 1H, NH, exchangeable with D_2O). Anal. ($C_{14}H_8N_2O_4S$)

3-Ethyl-6-(4-nitrobenzoyl)-1,3-benzothiazol-2(3*H*)-one (2). In a 100 ml round-bottom flask, dissolve 2.5 g (8.3 mmol) of 6-(4-nitrobenzoyl)-1,3-benzothiazol-2(3*H*)-one in 25 ml of acetone. Add 3.5 g (25 mmol) of potassium carbonate and heat to 60 °C for 1 hour. Add drop by drop and with magnetic stirring 0.08 ml (10 nmol) of iodoethane. Stir at ambient temperature for 6 hours. The reaction mixture acetone is evaporated.
Add 70 ml of water and 6 N HCl until an acid pH is reached. Spin out the precipitate formed, wash with water, dry it and recrystallise it with acetonitrile (2.33 g, 85%). Rf = 0.69 (EtOAc/Cyclohexane = 5/5): mp 148-152 °C; ir γ CO 1678 cm^{-1}, 1622 cm^{-1}, NO_2 1518 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-d_6) δ 1.20 (t, 3H, CH_3), 4.00 (q, 2H, CH_2), 7.54 (d, 1H, H_4, J_{4-5} = 8.1 Hz), 7.77 (dd, 1H, H_5, J_{5-4} = 8.1 Hz, J_{5-7} = 1.8 Hz), 7.93 (d, 2H, $H_{3'}$, $H_{5'}$, J = 9 Hz), 8.17 (d, 1H, H_7, J_{7-5} = 1.8 Hz), 8.35 (d, 2H, $H_{2'}$, $H_{6'}$, J = 9 Hz). Anal. ($C_{16}H_{12}N_2O_4S$)

4-[(2-Oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)carbonyl]benzonitrile (3). It is identical to that described for the obtaining of (1) page 2. 2(3*H*)-benzoselenazolone (5 g, 25 mmol), dimethylformamide (4.5 ml, 58 mmol), aluminium chloride (26.9 g, 202 mmol) and 4-cyanobenzoyl chloride (6.58 g, 30 mmol), the product 3 obtained and recrystallised in acetonitrile (4.1 g, 50%). Rf = 0.41 (EtOAc/Cyclohexane = 4/6): mp 230-232 °C; ir γ NH 3248 cm^{-1}, CN 2229 cm^{-1}, CO 1701 cm^{-1}, 1678 cm^{-1} 1H-NMR(300MHz,DMSO-d_6) δ 7.22 (d, 1H, H_4, J_{4-5} = 9.0 Hz), 7.67-7.70 (m, 1H, H_5), 7.82 (d, 2H, H_3, $H_{5'}$, J = 8.1 Hz), 8.00 (d, 2H, H_2, H_6 J=8.1 Hz),

8.16 (s, 1H, H_7), 12.18 (br s, 1H, NH, exchangeable with D_2O). Anal. ($C_{15}H_{18}N_2O_2Se$)

4-[(2-Methyl-2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)carbonyl] benzonitrile (4). It is identical to that described for the obtaining of (1) page 2. 3-methyl-2(3*H*)-benzoselenazolone (5 g, 24 mmol), dimethylformamide (4.2 ml, 54 mmol), aluminium chloride (25 g, 189 mmol) and 4-cyanobenzoyl chloride (4.7 g, 28 mmol), the product 4 obtained and recrystallised in acetonitrile (6.4 g, 80%). Rf = 0.51 (EtOAc/Cyclohexane = 4/6): mp 205-210 °C; ir γ CN 2231 cm^{-1}, CO 1699 cm^{-1}, 1658 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-d_6) δ 3.45 (s, 3H, CH_3), 7.45 (d, 1H, H_4, J_{4-5} = 8.1 Hz), 7.76- 7.78 (m, 1H, H_5), 7.83 (d, 2H, $H_{3'}$, $H_{5'}$, J = 8.1 Hz), 8.02 (d, 2H, $H_{2'}$, $H_{6'}$, J = 8.1 Hz), 8.25 (s, 1H, H_7). Anal. ($C_{16}H_{10}N_2O_2Se$)

4-[(3-Ethyl-2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl) carbonyl] benzonitrile (5). It is identical to that described for the obtaining of (2) page 2. 4-[(2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)carbonyl]benzonitrile (1.2 g, 3.7 mmol), acetone (50 ml), potassium carbonate (1.52 g, 11 mmol) and iodoethane (0.35 ml, 4.4 mmol), the product 5 obtained and recrystallised in acetonitrile (1.1 g, 87%). Rf = 0.55 (EtOAc/Cyclohexane = 4/6): mp 130-135 °C; ir γ CN 2231 cm^{-1}, CO 1697 cm^{-1}, 1674 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-d_6) δ 1.19 (t, 3H, CH_3), 4.00 (q, 2H, CH_2), 7.50 (d, 1H, H_4, J_{4-5} = 8.4 Hz), 7.76 (dd, 1H, H_5, J_{5-4} = 8.4 Hz, J_{5-7} = 1.5 Hz), 7.85 (d, 2H, $H_{3'}$, $H_{5'}$, J = 8.4 Hz), 8.02(d, 2H, $H_{2'}$, $H_{6'}$, J = 8.4 Hz), 8.27(s, 1H, H_7). Anal. ($C_{17}H_{12}N_2O_2Se$)

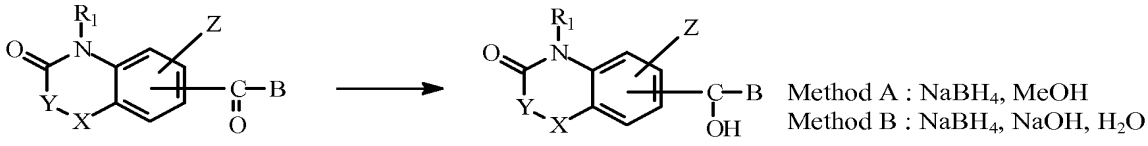
6-(4-Nitrobenzoyl)-1,3-benzoselenazol-2(3*H*)-one (6). It is identical to that described for the obtaining of (1) page 2. 3-methyl-2(3*H*)-benzoselenazolone (5 g, 24 mmol), dimethylformamide (4.2 ml, 54 mmol), aluminium chloride (25 g, 189 mmol) and 4-nitrobenzoyl

chloride (5.62 g, 30 mmol), the product 6 obtained and recrystallised in acetonitrile (6.2 g, 70%). Rf = 0.45 (EtOAc/Cyclohexane = 4/6): mp 241-245 °C; ir γ NH 3250 cm^{-1}, CO 1695 cm^{-1}, 1647 cm^{-1}, NO_2 1520 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-d_6) δ 7.25 (d, 1H, H_4, J_{4-5} = 8.4 Hz), 7.70 (dd, 1H, H_5), J_{5-4} = 8.4 Hz, $J_{5-7'}$ = 1.5 Hz, 7.91 (d, 2H, $H_{3'}$, $H_{5'}$, J = 9.0 Hz), 8.18 (d, 1H, H_7, J_{7-5} = 1.5 Hz), 8.35 (d, 2H, H_2, H_6, J = 9.0 Hz), 12.2 (br s, 1H, NH, exchangeable with D_2O). Anal. ($C_{14}H_8N_2O_4Se$)

3-Methyl-6-(4-nitrophenyl)-1,3-benzoselenazol-2(3*H*)-one (7). It is identical to that described for the obtaining of (2) page 2. 6-(4-Nitrobenzoyl)-1,3-benzoselenazol-2(3*H*)-one (2.5 g, 7.2 mmol), acetone (100 ml), potassium carbonate (2.99 g, 22 mmol) and iodomethane (0.54 ml, 8.6 mmol), the product 7 obtained and recrystallised in acetonitrile (2.42 g, 93%). Rf = 0.37 (EtOAc/Cyclohexane = 3/7): mp 151-155 °C; ir γ CO 1680 cm^{-1}, 1655 cm^{-1}, NO_2 1520 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-d_6) δ 3.45 (s, 3H, CH_3), 7.44 (d, 1H, H_4, J = 8.7 Hz), 7.78 (dd, 1H, H_5, J_{5-4} = 8.7 Hz, J_{5-7} = 1.8 Hz), 7.92 (d, 2H, $H_{3'}$, $H_{5'}$, J = 9.0 Hz), 8.28 (d, 1H, H_7, J_{7-5} = 1.8 Hz), 8.36 (d, 2H, $H_{2'}$, $H_{6'}$, J = 9.0 Hz). Anal. ($C_{15}H_{10}N_2O_4Se$)

3-Ethyl-6-(4-nitrobenzoyl)-1,3-benzoselenazol-2(3H)-one (8). It is identical to that described for the obtaining of (2) page 2. 6-(4-Nitrobenzoyl)-1,3-benzoselenazol-2(3H)-one (2.5 g, 7.2 mmol), acetone (100 ml), potassium carbonate (2.99 g, 22 mmol) and iodoethane (0.69 ml, 8.6 mmol), the product 8 obtained and recrystallised in methanol (2.2 g, 82%). Rf = 0.60 (EtOAc/Cyclohexane = 4/6): mp 97-102 °C; ir γ CO 1678 cm^{-1}, 1657 cm^{-1}, NO_2 1520 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-d_6) δ 1.20 (t, 3H, CH_3), 4.01 (q, 2H, CH_2), 7.51 (d, 1H, H_4, J_{4-5} = 8.4 Hz), 7.78 (dd, 1H, H_5, J_{5-4} = 8.4 Hz, J_{5-7} = 1.5 Hz), 7.94 (d, 2H, $H_{3'}$, $H_{5'}$, J = 8.7 Hz), 8.30 (d, 1H, H_7, J_{7-5} = 1.5 Hz), 8.37 (d, 2H, $H_{2'}$, $H_{6'}$, J = 8.7 Hz). Anal. ($C_{16}H_{12}N_2O_4Se$)

Reduction (Table III-B)



Ref	R_1	X	Y	Z	Isomer	B	Method
1a	CH_2CH_3	S	–	H	6	NO_2	A
2a	H	Se	–	H	6	CN	A
3a	CH_3	Se	–	H	6	CN	A
4a	CH_2CH_3	Se	–	H	6	CN	A
5a	CH_3	Se	–	H	6	NO_2	A
6a	CH_2CH_3	Se	–	H	6	NO_2	A

3-Ethyl-6-[hydroxy(4-nitrophenyl)methyl]-1,3-benzothiazol-2(3*H*)-one (1a). In a 100 ml round-bottom flask containing 2.3 g (7 mmol) of 3-ethyl-6-(4-nitrobenzoyl)-1,3-benzothiazol-2(3*H*)-one (2.3 g, 7 mmol), add 30 ml of methanol. Then, add little by little and with magnetic stirring, 0.3 g (7 mmol) of sodium borohydride. Continue stirring for 2 hours at ambient temperature. Evaporate all the solvent in a rotary evaporator, then take up the residue in 50 ml of slightly acid water. Spin out the precipitate formed, wash with water, until the wash water is neutral. Dry the product obtained and recrystallise it in ethyl acetate (2.2 g, 96%). Rf = 0.4 (EtOAc / Cyclohexane = 5/5); mp 160-162 °C; ir γ OH 3423cm^{-1}, CO 1647cm^{-1}, NO_2 1520 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.14 (t, 3H, CH_3), 3.90 (q, 2H, CH_2), 5.89 (s, 1H, CH), 6.30 (s, 1H, OH, exchangeable with D_2O), 7.30 (d, 1H, H_4, $J_{4\text{-}5}$ = 8.1 Hz), 7.37-7.40 (m. 1H, H_5), 7.66-7.68 (m, 3H, H_7, $H_{3'}$, $H_{5'}$), 8.16 (d, 2H, $H_{2'}$, $H_{6'}$, J = 8.1 Hz). Anal. ($C_{16}H_{14}N_2O_4S$)

4-[Hydroxy(2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)methyl]benzonitrile (2a). It is identical to that described for the obtaining of (1a) page 4. 4-[(2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)carbonyl]benzonitrile (2 g, 6.1 mmol), methanol (30 ml) and sodium borohydride (0.5 g, 6.1 mmol), the product 2a obtained and recrystallised in acetonitrile. (1.4 g, 70%). Rf = 0.37 (EtOAc/Cyclohexane = 5/5): mp 209-213 °C; ir γ OH 3506 cm^{-1}, NH 3146 cm^{-1}, CN 2227 cm^{-1}, CO 1695 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-d_6) δ 5.76 (s, 1H, CH), 6.17(s, 1H, OH, , exchangeable with D_2O), 7.02 (d, 1H, H_4, J_{4-5} = 8.1 Hz), 7.25 (dd, 1H, H_5, J_{5-4} = 8.1 Hz, J_{5-7} = 1.5 Hz), 7.54 (d, 3H, $H_{3'}$, $H_{5'}$, J = 8.1 Hz), 7.66 (d, 2H, $H_{2'}$, $H_{6'}$, J = 8.1 Hz), 7.43 (d, 1H, H_7, J_{7-5} = 1.5 Hz), 11.85 (br s, 1H, NH, exchangeable with D_2O). Anal. ($C_{15}H_{10}N_2O_2Se$)

4-[Hydroxy(3-methyl-2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)methyl]benzonitrile (3a). It is identical to that described for the obtaining of (1a) page 4. 4-[(3-Methyl-2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)carbonyl] benzonitrile (2.0 g, 5.9 mmol), methanol (50 ml) and sodium borohydride (1.2 g, 32 mmol), the product 3a obtained and recrystallised in ethyl acetate (1.8 g, 90%). Rf = 0.38 (EtOAc/Cyclohexane = 5/5); mp 205-208 °C; ir γ OH 3472 cm^{-1}, CN 2224 cm^{-1}, CO 1651 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-d_6) δ 3.30 (s, 3H, CH_3), 5.80 (s, 1H, CH), 5.82 (s, 1H, OH, exchangeable with D_2O), 7.19 (d, 1H, H_4, J_{4-5} = 8.4 Hz), 7.34-7.36 (m, 1H, H_5), 7.55 (d, 2H, $H_{3'}$, $H_{5'}$, J = 7.8 Hz), 7.73-7.77 (m, 3H, H_7, $H_{2'}$, $H_{6'}$). Anal. ($C_{16}H_{12}N_2O_2Se$)

4-[(3-Ethyl-2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)(hydroxy) methyl]benzonitrile (4a).

It is identical to that described for the obtaining of (1a) page 4. 4-[(3-ethyl-2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)carbonyl]benzonitrile (1.1 g, 3.0 mmol), methanol (15 ml) and sodium borohydride (0.06 g,

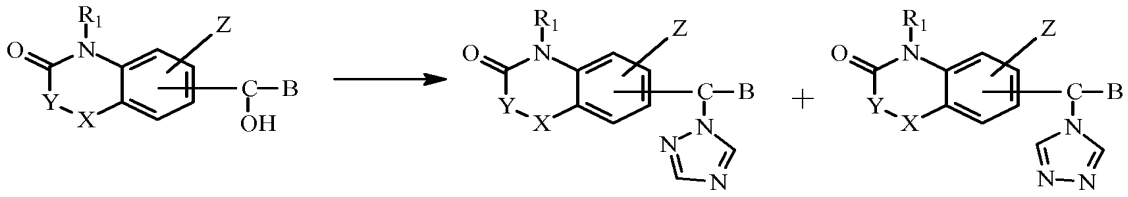
1.5 mmol), the product 4a obtained and recrystallised in ethyl acetate (0.92 g, 86%). Rf = 0.31 (EtOAc/Cyclohexane = 4/6): mp 132-134 °C; ir γ OH 3427 cm^{-1}, CN 2227 cm^{-1}, CO 1641 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-d_6) δ 1.13 (t, 3H, CH_3), 3.89 (q, 2H, CH_2), 5.80 (d, 1H, CH, J = 3.9 Hz), 6.19 (d, 1H, OH, J = 3.6 Hz, , exchangeable with D_2O), 7.26 (d, 1H, H_4, J_{4-5} = 8.1 Hz), 7.34 (dd, 1H, H_5, J_{5-4} = 8.1 Hz, J_{5-7} = 1.8 Hz), 7.57 (d, 2H, $H_{3'}$, $H_{5'}$, J = 8.4 Hz), 7.75-7.79 (m, 3H, H_7, $H_{2'}$, $H_{6'}$). Anal. ($C_{17}H_{14}N_2O_2Se$)

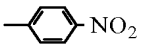
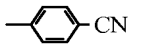
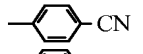
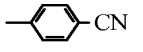
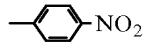
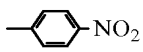
6-[Hydroxy(4-nitrophenyl)methyl]-3-methyl-1,3-benzoselenazol-2(3*H*)-one (5a). It is identical to that described for the obtaining of (1a) page 4. 3-Methyl-6-(4-nitrophenyl)-1,3-benzoselenazol-2(3*H*)-one (2.3 g, 6.4 mmol), methanol (30 ml) sodium borohydride (0.3 g, 6.4 mmol), the product 5a obtained and recrystallised in acetonitrile (1.9 g, 84%). Rf = 0.31 (EtOAc / Cyclohexane = 4/6); mp 182-183 °C; ir γ OH 3406 cm^{-1}, CO 1645 cm^{-1}, NO_2 1512 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.35 (s, 3H, CH_3), 5.88 (s, 1H, CH), 6.29 (s, 1H, OH, exchangeable with D_2O), 7.21 (d, 1H, H_4, J_{4-5} = 8.1 Hz), 7.37 (dd, 1H, H_5, J_{5-4} = 8.1 Hz, J_{5-7} = 1.8 Hz), 7.64 (d, 2H, $H_{3'}$, $H_{5'}$, J = 8.7 Hz), 7.75 (d, 1H, H_7, J_{7-5} = 1.8 Hz), 8.16 (d, 2H, $H_{2'}$, $H_{6'}$, J = 8.7 Hz). Anal. ($C_{15}H_{12}N_2O_4Se$)

3-Ethyl-6-[hydroxy(4-nitrophenyl)methyl]-1,3-benzoselenazol-2(3*H*)-one (6a). It is identical to that described for the obtaining of (1a) page 4. 3-Ethyl-6-(4-nitrobenzoyl)-1,3-benzoselenazol-2(3*H*)-one (2.2 g, 5.8 mmol), methanol (30 ml) sodium borohydride (0.3 g, 5.8 mmol), the product 6a obtained and recrystallised in ethyl acetate (1.2 g, 57%). Rf = 0.35 (EtOAc / Cyclohexane = 4/6); mp 135-137 °C; ir γ OH 3420 cm^{-1}, CO 1653 cm^{-1}, NO_2 1514 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13 (t, 3H, CH_3), 3.89 (q, 2H, CH_2), 5.87 (s, 1H, CH), 6.28 (s, 1H, OH, exchangeable with D_2O), 7.27 (d, 1H, H_4, J_{4-5} = 8.4 Hz), 7.36 (dd, 1H, H_5,

$J_{5\text{-}4}$ = 8.4 Hz, $J_{5\text{-}7}$ = 1.8 Hz), 7.65(d, 2H, $H_{3'}$, $H_{5'}$, J = 9 Hz), 7.76 (d, 1H, H_7, $J_{7\text{-}5}$ = 1.8 Hz), 8.17-8.20 (m, 2H, $H_{2'}$, $H_{6'}$). Anal. ($C_{16}H_{14}N_2O_4Se$)

Substitution



Ref	R_1	X	Y	Z	Isomère	triazole	B
1b	CH_2CH_3	S	—	H	6	1,2,4	
2b	H	Se	—	H	6	1,2,4	
3b	CH_3	Se	—	H	6	1,2,4	
4b	CH_2CH_3	Se	—	H	6	1,2,4	
5b	CH_3	Se	—	H	6	1,2,4	
6b	CH_2CH_3	Se	—	H	6	1,2,4	

EXAMPLE 44:

3-Ethyl-6-[(4-nitrophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-benzothiazol-2(3*H*)-one.

In a 100 ml round-bottom flask, dissolve 4.83 g (70 mmol) of 1*H*-1,2,4-triazol in 35 ml of acetonitrile then slowly add 1.3 ml (18 mmol) of thionyl chloride. Continue stirring for 30 minutes at ambient temperature. Collect the filtrate obtained. The filtrate is added drop by drop to a solution of 1.5 g (4.5 mmol) of 3-ethyl-6-[hydroxy(4-nitrophenyl)methyl]-1,3-benzothiazol-2(3*H*)-one and 10 ml of acetonitrile. Continue stirring for 5 hours at ambient temperature. Evaporate the solvent in a rotary evaporator: Add 100 ml of water and add 6 N HCl until an acid pH is

reached. Extract with 150 ml of ethyl acetate. The aqueous phase is alkalized with a solution of potassium carbonate as far as neutral. Extract with 150 ml of ethyl acetate, dry the organic phase on $MgSO_4$ then vaporize it and purify it by chromatography on silica gel. (eluant: EtOAc) (0.34 g, 20%). Rf = 0.28 (EtOAc): mp 79-83 °C; ir γ CO 1676 cm^{-1}, 1602 cm^{-1}, NO_2 1520 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.17 (t, 3H, CH_3), 3.93 (q, 2H, CH_2), 7.30-7.35 (m, 2H, CH, H_4), 7.40-7.47 (m, 3H, H_5, $H_{3'}$, $H_{5'}$), 7.62 (s, 1H, H_7), 8.12 (s, 1H, $H_{triazole}$), 8.23 (d, 2H, $H_{2'}$, $H_{6'}$, J = 8.1 Hz), 8.69 (s, 1H, $H_{triazole}$). Anal. ($C_{17}H_{13}N_5O_3S$)

EXAMPLE 45:

4-[(2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)(1*H*-1,2,4-triazol-1-yl)methyl]benzonitrile . It is identical to that described for the obtaining of (1b) page 6. 4-[Hydroxy(2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)methyl]benzonitrile (1.5 g, 4.6 mmol), thionyl chloride (1.3 ml, 18 mmol), 1*H*-1,2,4-triazol (4.84 g, 70 mmol) and THF (35 ml), the product 2b obtained and purified by silica gel chromatography (eluant: EtOAc) (0.17 g, 10%). Rf = 0.46 (EtOAc): mp 223-226 °C; ir γ NH 3435 cm^{-1}, CN 2229 cm^{-1}, CO 1685 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-d_6) δ 7.09 (d, 1H, H_4, J_{4-5} = 8.1 Hz), 7.13 (dd, 1H, H_5, J_{5-4} = 8.1 Hz, J_{5-7} = 1.5 Hz), 7.20 (s, 1H, CH), 7.33 (d, 2H, $H_{3'}$, $H_{5'}$, J = 7.8 Hz), 7.56 (d, 1H, H_7, J_{7-5} = 1.5 Hz), 7.83 (d, 2H, $H_{2'}$, $H_{6'}$, J = 7.8 Hz), 8.08 (s, 1H, $H_{triazole}$), 8.62 (s, 1H, $H_{triazole}$), 11.83 (br s, 1H, NH, exchangeable with D_2O). Anal. ($C_{17}H_{11}N_5OSe$)

EXAMPLE 46:

4-[(3-Methyl-2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)(1*H*-1,2,4-triazol-1-yl)methyl]benzonitrile. It is identical to that described for the obtaining of (1b) page 6. 4-[Hydroxy(3-methyl-2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)methyl]benzonitrile (1.5 g, 4.4 mmol), thionyl

chloride (1.3 ml, 18 mmol), 1*H*-1,2,4-triazol (4.65 g, 67 mmol) and acetonitrile (40 ml), the product 2b obtained and purified by silica gel chromatography (eluant: EtOAc) (0.35 g, 20%). Rf = 0.42 (EtOAc): mp 154-158 °C; ir γ CN 2229 cm^{-1} CO 1657 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-d_6) δ 3.37 (s, 3H, CH_3), 7.25-7.30 (m, 3H, CH, H_4, H_5), 7.34 (d, 2H, $H_{3'}$, $H_{5'}$, *J* = 8.7 Hz), 7.66 (s, 1H, H_7), 7.84 (d, 2H, $H_{2'}$, $H_{6'}$, *J* = 8.7 Hz), 8.09 (s, 1H, $H_{triazole}$), 8.64 (s, 1H, $H_{triazole}$). Anal. ($C_{18}H_{13}N_5OSe$)

EXAMPLE 47:

4-[(3-Ethyl-2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)(1*H*-1,2,4-triazol-1-yl)methyl] benzonitrile. It is identical to that described for the obtaining of (1b) page 6. 4-[(3-Ethyl-2-oxo-2,3-dihydro-1,3-benzoselenazol-6-yl)(hydroxy)methyl]benzonitrile (0.9 g, 2.5 mmol), thionyl chloride (0.7 ml, 10 mmol), 1*H*-1,2,4-triazol (2.68 g, 39 mmol) and acetonitrile (35 ml), the product 2b obtained and purified by silica gel chromatography (eluant: EtOAc) (0.2 g, 19%). Rf = 0.44 (EtOAc); mp 95-98 °C; ir γ CN 2229 cm^{-1}, CO 1670 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.15 (t, 3H, CH_3), 3.91 (q, 2H, CH_2), 7.26 (m, 2H, CH, H_4), 7.35-7.39 (m, 3H, H_5, $H_{3'}$, $H_{5'}$), 7.69 (s, 1H, H_7), 7.86 (d, 2H, $H_{2'}$, $H_{6'}$, *J* = 8.1 Hz), 8.11 (s, 1H, $H_{triazole}$), 8.67 (s, 1H, $H_{triazole}$). Anal. ($C_{19}H_{15}N_5OSe$)

EXAMPLE 48

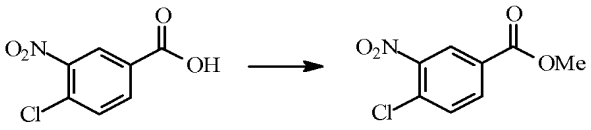
3-Methyl-6-[(4-nitrophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1,3-benzoselenazol-2(3H)-one. It is identical to that described for the obtaining of (1b) page 6. 6-[Hydroxy(4-nitrophenyl)methyl]-3-methyl-1,3-benzoselenazol-2(3*H*)-one (1.5 g, 4.1 mmol), thionyl chloride (1.γ ml, 17 mmol), 1*H*-1,2,4-triazol (4.39 g, 64 mmol) and acetonitrile (40 ml), the product 2b obtained and purified by silica gel chromatography (eluant: EtOAc) (0.29 g, 17%). Rf = 0.46 (EtOAc); mp 190-195 °C; ir γ CO 1651 cm^{-1}, NO_2 1520 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.36 (s, 3H, CH_3), 7.30-7.35 (m, 3H, CH, H_4, H_5), 7.44 (d, 2H, $H_{3'}$, $H_{5'}$, *J* = 8.7), 7.69 (s,

1H, H_7), 8.12 (s, 1H, $H_{triazole}$), 8.24 (d, 2H, $H_{2'}$, $H_{6'}$, J = 8.7), 8.68 (s, 1H, $H_{triazole}$). Anal. ($C_{17}H_{13}N_5O_3Se$)

EXAMPLE 49

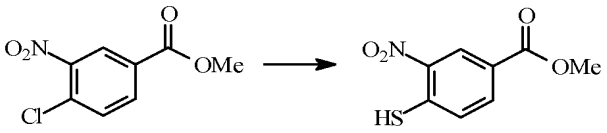
3-Ethyl-6-[(4-nitrophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1,3-benzoselenazol-2(3H)-one. It is identical to that described for the obtaining of (1b) page 6. 3-ethyl-6-[Hydroxy(4-nitrophenyl)methyl]-1,3-benzoselenazol-2(3*H*)-one (1.2 g, 3.2 mmol), thionyl chloride (0.9 ml, 13 mmol), 1*H*-1,2,4-triazol (3.38 g, 49 mmol) and acetonitrile (35 ml), the product 2b obtained and purified by silica gel chromatography (eluant: EtOAc) (0.28 g, 21%). Rf = 0.44 (EtOAc): mp 79-82 °C; ir γ CO 1670 cm^{-1}, NO_2 1520 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.13 (t, 3H, CH_3), 3.91 (q, 2H, CH_2), 7.27-7.39 (m, 3H, CH, H_4, H_5), 7.45 (d, 2H, $H_{3'}$, $H_{5'}$, J = 8.7 Hz), 7.70 (s, 1H, H_7), 8.12 (s, 1H, $H_{triazole}$), 8.24 (d, 2H, $H_{2'}$, $H_{6'}$, J = 8.7 Hz), 8.69 (s, 1H, $H_{triazole}$) Anal. ($C_{18}H_{15}N_5O_3Se$)

PREPARATION OF COMPOUNDS OF EXAMPLES 50 to 51 (Tables I-B, III-B, IV)

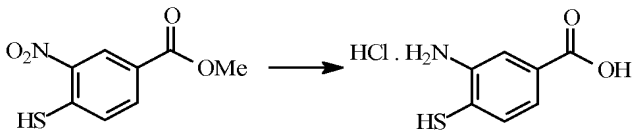


Methyl 4-chloro-3-nitrenzoate (1). Dissolve 4-chloro-3-nitro-benzoic acid (5.0 g, 24.8 mmol) in 200 ml of methanol and add 4.15 ml (29.8 mmol) of triethylamine. Cool in an ice-salt bath and add drop by drop 3.19 ml (44.7 mmol) of acetyl chloride. Agitate at reflux for 6 hours. Evaporate the solvent under reduced pressure. Take up the residue with 100 ml of water and extract 2 times with ethyl acetate (100 ml). Dry the organic phase on $MgSO_4$ and vaporize it under reduced pressure and purify it with ether (10 ml) (4.81 g, 92%). Rf = 0.55 (EtOAc/Cyclohexane

= 7/3); mp 79-80 °C; ir. CO 1716 cm^{-1}; ^{1}H-NMR(300MHz, DMSO-d_6) δ 3.90 (s, 3H, OCH_3), 7.90 (d, 1H, H_5, J_{5-6} = 8.1 Hz), 8.15 (dd, 1H, H_6, J_{6-5} = 8.1 Hz, J_{5-2} = 1.5 Hz), 8.49(d, 1H, H_2, J_{2-6} = 1.5 Hz). Anal. ($C_8H_6ClNO_4$).

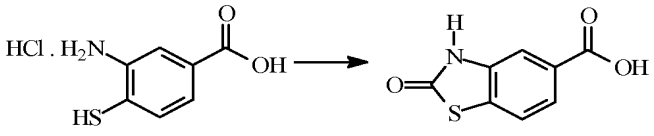


Methyl-3-nitro-4-sulfanylbenzoate (2). In a 250 ml round-bottom flask, put into suspension sodium sulphate (2.7 g, 34 mmol) and methyl-4-chloro-3-nitrobenzoate (5 g, 23 mmol) in 150 ml of absolute ethanol. Stir at ambient temperature for 7 hours. Pour the reaction mixture on ice (200 ml). Add acetic acid as far as pH 2 and extract 3 times with CH_2Cl_2 (100 ml). Dry the organic phase on $MgSO_4$ and vaporize it under reduced pressure and purify it with ether (3.9 g, 80%). Rf = 0.31 (EtOAc/Cyclohexane = 3/7); mp 98-101 °C; ir. SH 2546, CO 1722 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H, OCH_3), 4.31 (br s, 1H, SH, exchangeable with D_2O), 7.82 (d, 1H, H_5, J_{5-6} = 8.2 Hz), 8.17 (dd, 1H, H_6, J_{6-5} = 8.2 Hz, , J_{5-2} = 1.5 Hz), 8.41 (d, 1H, H_2, J_{2-6} = 1.5 Hz). Anal. ($C_8H_7NO_4S$).

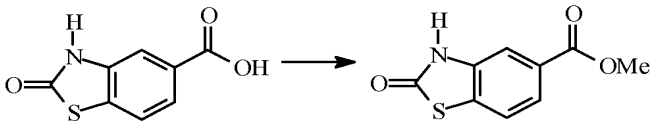


3-Amino-4-sulfanyl benzoic acid hydrochloride (3). In a 250 ml round-bottom flask, put into suspension tin(II) chloride (17.3 g, 91.4 mmol) and methyl-3-nitro-4-sulfanylbenzoate (3.9 g, 18.3 mmol) in 50 ml of 6 N HCl. Agitate by reflux for 4 hours. Pour the reaction mixture on ice (200 ml).

Spin out the precipitate formed, dry it and recrystallise it with ether (3.3 g, 81%). Rf = 0.32 (EtOAc/Cyclohexane = 5/5); mp 215-217 °C (decomposition); ir NH_2 3331 cm^{-1}, SH 2511 cm^{-1}, CO 1711 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 4.42 (br s, 1H, SH, exchangeable with D_2O), 7.76 (d, 1H, H_5, J_{5-6} = 8.2 Hz), 8.31 (dd, 1H, H_6, J_{6-5} = 8.1 Hz, J_{5-2} = 1.5 Hz), 8.44(d, 1H, H_2, J_{2-6} = 1.5 Hz), 12.2 (br s, 1H, OH, exchangeable with D_2O). Anal. ($C_8H_{10}NO_2ClS$).

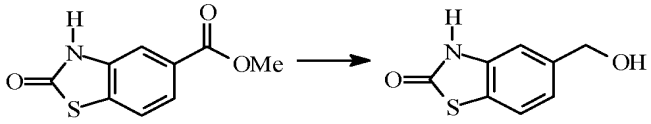


2-Oxo-2,3-dihydro-1,3-benzothiazolone-5-carboxylic acid (4). Mix 5 g (24.3 mmol) of 3-amino-4-sulfanyl benzoic acid HCl salt and 14.6 g (243 mmol) of urea. Stir at 140-145 °C for 4 hours. Pour the reaction mixture on ice (200 ml) and add 6N acetic acid as far as pH 2. Spin out the precipitate formed, dry it and recrystallise it with ether (2.9 g, 49%). Rf = 0.65 (MeOH/EtOH/Cyclohexane = 3/5/2), mp 275-277 °C; ir OH 3099 cm^{-1}, CO 1718 cm^{-1}, NCO 1682 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.62 (s, 1H, H_4), 7.69-7.72 (m, 2H, $H_{5,6}$), 12.10(br s, 1H, NH, exchangeable with D_2O), 13.06 (br s, 1H, exchangeable with D_2O). Anal. ($C_9H_7NO_3S$).

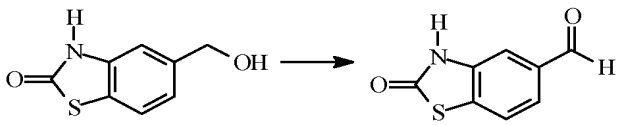


Methyl-2-oxo-2,3-benzothiazolone-5-carboxylate (5). Put the 2-oxo-2,3-dihydro-1,3-benzothiazolone-5-carboxylic acid (5.0 g, 24.8 mmol) in 200 ml of methanol. Cool in an ice-salt bath at 0 °C and add drop by drop

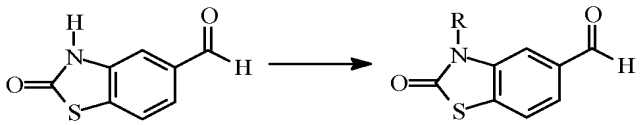
9.34 ml (128.1 mmol) of thionyl chloride. Agitate by reflux for 5 hours. Evaporate the solvent under reduced pressure. Take up the residue with 100 ml of water and extract 2 times with ethyl acetate (100 ml). Dry the organic phase on $MgSO_4$ and vaporize it under reduced pressure and purify it with ether (10 ml) (4.0 g, 75%). Rf = 0.58 (EtOAc/Cyclohexane = 5/5); mp 217-219 °C; ir CO 1695 cm^{-1}, NCO 1684 cm^{-1}; ^{1}H-NMR(300MHz, DMSO-d_6) δ 3.85 (s, 3H, OCH_3), 7.60 (d, 1H, H_4, J_{4-6}= 2.7 Hz), 7.67-7.69 (m, 2H, $H_{6,7}$), 12.13 (br s, 1H, NH, exchangeable with D_2O). Anal. ($C_9H_7NO_3S$).



5-(Hydroxymethyl)-1,3-benzothiazol-2(3H)-one (6). Dissolve the methyl-2-oxo-2,3-benzothiazolone-5-carboxylate (5.0 g, 23.9 mmol) in 100 ml of THF. Cool in an ice-salt bath and add little by little 1.1 g (28.7 mmol) of $LiAlH_4$. Stir at ambient temperature for 3 hours. Slowly add 100 ml of water to the reaction mixture and add 1 N acetic acid as far as pH 7. Extract 2 times with CH_2Cl_2 (100 ml). Dry the organic phase on $MgSO_4$ and vaporize it under reduced pressure and purify it with ether (10 ml) (3.4 g, 79%). Rf = 0.33 (EtOAc/ Cyclohexane = 3/7); mp 178-181 °C; ir OH 3319 cm^{-1}, NCO 1684 cm^{-1}; ^{1}H-NMR(300MHz, DMSO-d_6) δ 4.49 (d, 2H, CH_2OH, J = 5.7 Hz), 5.26 (t, 1H, CH_2OH, J = 5.7 Hz, exchangeable with D_2O), 7.02 (d, 1H, H_6, J_{6-7} = 8.1 Hz), 7.09 (s, 1H, H_4), 7.45 (d, 1H, H_7, J_{7-6} = 8.1 Hz), 11.85 (s, 1H, NH, exchangeable with D_2O). Anal. ($C_8H_7NO_2S$).



2-Oxo-2,3-dihydro-1,3-benzothiazol-5-carbaldehyde (7). Dissolve the 5-(hydroxymethyl)-1,3-benzothiazol-2(3*H*)-one (1 g, 5.5 mmol) in 100 ml of CH_2Cl_2. Add 10 g (177 mmol) manganese dioxide and stir at ambient temperature for 4 hours. Spin the reaction mixture and evaporate the solvent under reduced pressure and purify it with ether (10 ml) (0.69 g, 69%). Rf = 0.56 (EtOAc/Cyclohexane = 5/5); mp 211-215 °C; ir CO 1730 cm^{-1}, NCO 1691 cm^{-1}; ^{1}H-NMR(300MHz, DMSO-d_6) δ 7.53 (s, 1H, H_4), 7.65 (d, 1H, H_6, $J_{6\text{-}7}$ = 8.1 Hz), 7.80 (d, 1H, H_7, $J_{7\text{-}6}$ = 8.1 Hz), 9.95 (s, 1H, COH), 12.22 (br s, 1H, NH, exchangeable with D_2O). Anal. ($C_8H_5NO_2S$).

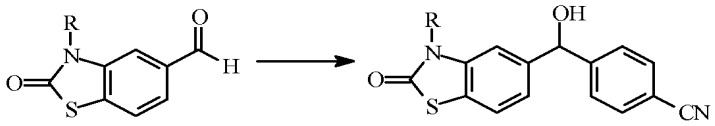


Ref	R	yield
8a	CH_3	84%
8b	CH_2CH_3	87%

3-Methyl-2-oxo-2,3-dihydro-1,3-benzothiazol-5-carbaldehyde (8a). In a 100 ml round-bottom flask, dissolve 1.0 g (5.6 mmol) of 2-oxo-2,3-dihydro-1,3-benzothiazol-5-carbaldehyde in 50 ml of acetone. Add 2.3 g (16.7 mmol) of potassium carbonate and 0.42 ml (6.7 mmol) of iodomethane. Stir at ambient temperature for 3 hours. The reaction mixture acetone is evaporated. Add 100 ml of water and extract 2 times with ethyl acetate (100 ml). Dry the organic phase on $MgSO_4$ and vaporize it under reduced pressure and purify it with ether (10 ml) (0.91 g, 84%). Rf = 0.59 (EtOAc/Cyclohexane = 5/5); mp 140-142 °C; ir CO 1682 cm^{-1}, NCO 1674 cm^{-1}; ^{1}H-NMR(300MHz, DMSO-d_6) δ 3.46 (s,

3H, NCH_3), 7.73-7.75 (m, 2H, $H_{4,6}$), 7.90 (d, 1H, H_7, $J_{7\text{-}6}$ = 8.1 Hz), 9.99 (s, 1H, COH). Anal. ($C_9H_7NO_2S$).

3-Ethyl-2-oxo-2,3-dihydro-1,3-benzothiazol-5-carbaldehyde (8b). It is identical to that described to obtain (8a). 2-Oxo-2,3-dihydro-1,3-benzothiazol-5-carbaldehyde (2 g, 11.1 mmol), potassium carbonate (4.6 g, 33.3 mmol), iodoethane (1.1 ml, 13.3 mmol) and acetone (50 ml), the product 8b obtained and purified with ether (2.01 g, 87%). Rf = 0.63 (EtOAc/Cyclo-hexane = 5/5); mp 155-156 °C; ir CO 1689 cm^{-1}, NCO 1664 cm^{-1}; ^{1}H-NMR(300MHz, DMSO-d_6) δ 1.23 (t, 3H, CH_2CH_3, J = 6.7 Hz), 4.03 (q, 2H, CH_2CH_3, J = 6.7 Hz), 7.74 (dd, 1H, H_6, $J_{6\text{-}7}$ = 8.1 Hz, $J_{6\text{-}4}$ = 2.1 Hz), 7.85 (d, 1H, H_4, $J_{4\text{-}6}$ = 2.1 Hz), 7.91 (d, 1H, H_7, $J_{7\text{-}6}$ = 8.1 Hz), 10.04 (s, 1H, COH). Anal. ($C_{10}H_9NO_2S$).



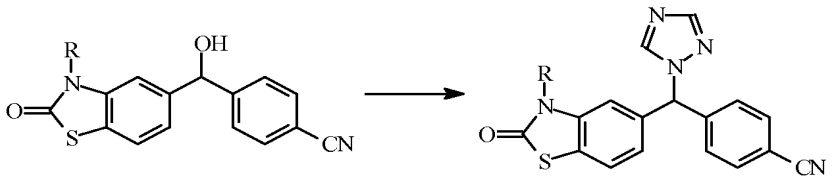
Ref	R	yield
9a	CH_3	18%
9b	CH_2CH_3	29%

4-[Hydroxy(3-methyl-2-oxo-2,3-dihydro-1,3-benzothiazol-5-yl)methyl]benzonitrile (9a).

Dissolve 4-bromobenzonitrile (1.9 g, 10.4 mmol) in 20 ml of THF and add 5.2 ml (10.4 mmol) of *i*-propyl magnesium chloride solution 2M in THF. Stir at ambient temperature for 2 hours. Next pour in drop by drop 2 g (10.4 mmol) of 3-methyl-2-oxo-2,3-dihydro-1,3-benzothiazol-5-carbaldehyde (2 g, 10.4 mmol) previously diluted in 20 ml of THF. Slowly add 100 ml of water into the reaction mixture and extract 2 times with ethyl acetate (100 ml). Dry the organic phase on $MgSO_4$ and vaporize it

under reduced pressure and purify it by silica gel chromatography. (eluant: EtOAc/C-hexane = 3/7) (0.55 g, 18%) Rf = 0.29 (EtOAc/Cyclohexane = 5/5); mp 183-186 °C; ir OH 3398 cm^{-1}, CN 2224 cm^{-1}, CO 1658 cm^{-1}; ^{1}H-NMR(300MHz, DMSO-d_6) δ 3.38 (s, 3H, NCH_3), 5.84 (d, 1H, CH, J = 3.9 Hz), 6.28 (d, 1H, OH, J = 3.9 Hz, exchangeable with D_2O), 7.16 (d, 1H, H_7, $J_{7\text{-}6}$ = 8.1 Hz), 7.36 (s, 1H, H_4), 7.54 (d, 1H, H_6, $J_{6\text{-}7}$ = 8.1 Hz), 7.60 (d, 2H, $H_{2',6'}$, $J_{2'\text{-}3'}$ = 8.1 Hz), 7.75 (d, 2H, $H_{3',5'}$, $J_{3'\text{-}2'}$ = 8.1 Hz). Anal. ($C_{16}H_{12}N_2O_2S$).

4-[Hydroxy(3-ethyl-2-oxo-2,3-dihydro-1,3-benzothiazol-5-yl)methyl]benzonitrile (9b). It is identical to that described to obtain (9a). 3-Ethyl-2-oxo-2,3-dihydro-1,3-benzothiazol-5-carbaldehyde (2g, 9.7 mmol), 4-bromobenzonitrile (1.7 g, 9.7 mmol), *i*-propyl magnesium chloride 2M solution in THF (4.8 ml, 9.7 mmol) and THF (40 ml), the product 9b obtained and purified by silica gel chromatography (eluant: EtOAc/C-hexane = 3/7) (0.87 g, 29%). Rf = 0.31 (EtOAc/ Cyclohexane = 5/5); mp 156-158 °C; ir OH 3433 cm^{-1}, CN 2227 cm^{-1}, NCO 1674 cm^{-1}; ^{1}H-NMR(300MHz, DMSO-d_6) δ 1.80 (t, 3H, CH_2CH_3, J = 7.2 Hz), 3.93 (q, 2H, CH_2CH_3, J = 7.2 Hz), 5.97 (d, 1H, CH, J = 3.9 Hz), 6.30 (d, 1H, OH, J = 3.9 Hz, exchangeable with D_2O), 7.17 (d, 1H, H_7, $J_{7\text{-}6}$ = 8.0 Hz), 7.45 (s, 1H, H_4), 7.56 (d, 1H, H_6, $J_{6\text{-}7}$ = 8.0 Hz), 7.62 (d, 2H, $H_{2',6'}$, $J_{2'\text{-}3'}$ = 8.1 Hz), 7.77 (d, 2H, $H_{3',5'}$, $J_{3'\text{-}2'}$ = 8.1 Hz). Anal. ($C_{17}H_{14}N_2O_2S$).



Ref	R	yield
10a	CH_3	32%
10b	CH_2CH_3	21%

EXAMPLE 50:

4-[(3-Methyl-2-oxo-2,3-dihydro-1,3-benzothiazol-5-yl)(1H-1,2,4-triazol-1-yl)methyl] benzonitrile. In a 100 ml round-bottom flask, dissolve 1.3 g (18.8 mmol) of 1*H*-1,2,4-triazol in 20 ml of acetonitrile then slowly add 0.37 ml (5.1 mmol) of thionyl chloride. Continue stirring for 30 minutes at ambient temperature. Spin the filtrate obtained. The filtrate is added drop by drop to a solution of 0.38 g (1.3 mmol) of 4-[hydroxy(3-methyl-2-oxo-2,3-dihydro-1,3-benzothiazol-5-yl)methyl]benzonitrile and 10 ml of acetonitrile. Continue stirring for 5 hours at ambient temperature. Evaporate the solvent in a rotary evaporator. Add 100 ml of water and add 6 N HCl until an acid pH is reached. Extract with 150 ml of ethyl acetate. The aqueous phase is alkalized with a solution of potassium carbonate as far as neutral. Extract with 150 ml of ethyl acetate, dry the organic phase on $MgSO_4$ then vaporise it and purify it by silica gel chromatography. (eluant: EtOAc/MeOH = 9/1) (0.14 g, 32%). Rf = 0.54 (EtOAc/MeOH = 9/1): mp 122-125 °C; ir: CN 2229 cm^{-1}, NCO 1680 cm^{-1}; ^{1}H-NMR(300MHz, DMSO-d_6) δ 3.34 (s, 3H, NCH_3), 7.10 (dd, 1H, H_6, J_{6-7} = 8.1 Hz, J_{6-4} = 1.5 Hz), 7.27-7.28 (m, 2H, CH, H_4), 7.35 (d, 2H, $H_{2',6'}$, $J_{2'-3'}$ = 8.4 Hz), 7.66 (d, 1H, H_7, J_{7-6} = 8.1 Hz), 7.84 (d, 2H, $H_{3',5'}$, $J_{3'-2'}$ = 8.4 Hz), 8.11 (s, 1H, $H_{triazole}$), 8.66 (s, 1H, $H_{triazole}$). Anal. ($C_{18}H_{13}N_5OS$).

EXAMPLE 51:

4-[(3-Ethyl-2-oxo-2,3-dihydro-1,3-benzothiazol-5-yl)(1H-1,2,4-triazol-1-yl)methyl] benzonitrile. It is identical to that described for the obtaining of (10a). 4-[Hydroxy(3-ethyl-2-oxo-2,3-dihydro-1,3-benzothiazol-5-yl)methyl] benzonitrile) (0.87 g, 2.8 mmol), 1,2,4-triazole (2.9 g, 42.0 mmol), thionyl chloride (0.82 ml, 1.1 mmol) and acetonitrile (100 ml), the product 2b obtained and purify it by silica gel

chromatography (eluant: EtOAc/MeOH = 9/1) (0.21 g, 21%). Rf = 0.58 (EtOAc/MeOH = 9/1); mp 125-127 °C; ir CN 2229 cm^{-1}, NCO 1674 cm^{-1}; ^{1}H-NMR(300MHz, DMSO-d_6) δ 1.12 (s, 3H, CH_2CH_3, J = 7.5 Hz), 3.88 (q, 2H, CH_2CH_3, J = 7.5 Hz), 7.10 (dd, 1H, H_6, J_{6-7} = 8.1 Hz, J_{6-4} = 1.5 Hz), 7.29 (s, 1H, CH), 7.35 (d, 2H, $H_{2',6'}$, $J_{2'-3'}$ = 8.1 Hz), 7.40 (s, 1H, H_4), 7.68 (d, 1H, H_7, J_{7-6} = 8.1 Hz), 7.86 (d, 2H, $H_{2',6'}$, $J_{2'-3'}$ = 8.1 Hz), 8.12 (s, 1H, $H_{triazole}$), 8.69 (s, 1H, $H_{triazole}$). Anal. ($C_{19}H_{15}N_5OS$).

The examples above illustrate the invention and do not limit it in any way. The preparations above also comprise the intermediates of synthesis useful for the preparation of the compounds of formula (I) of the invention.

PHARMACOLOGICAL STUDY (Table V)

Example A: Study of acute toxicity

The acute toxicity has been estimated after oral administration to groups of 8 mice (26 g). The animals were observed at regular intervals in the course of the first day and daily during the two weeks following treatment.

The dose at which 50% mortality in the animals (LD_{50}) is observed was measured and showed the low-level toxicity of the compounds of the invention.

Example B: Study of the power of the aromatase inhibitor in vitro

The IC_{50}, concentrations inhibiting 50% of the activity of the enzyme, were determined using microsomes from the human placenta as source of the enzyme according to the tritiated water method described by PURBA et al (1990).

The most active compounds deliver an IC_{50} close to 1 nanomolar.

Example C: Study of cellular cytotoxicity

The protocol of the study of cellular cytotoxicity is adapted after MOSMANN (1983).

It consists of the transformation of MTT to formazan by mitochondrial succinate dehydrogenase. This test is done on E293 cells of human embryonic kidney which do not express aromatase.

The results showed that the compounds are not cytotoxic.

Example D: Study of the activity *in vivo*

The activity *in vivo* of aromatase inhibition by compounds of formula (I) according to the invention has been tested according to the model established by Bharnagar et al. (1990).

In general, immature female rats of the Sprague-Dawley line of a weight ranging from 40 to 50 g have been treated with a dose of androstenedione at 30 mg/kg for 4 days, in the absence or in the presence of doses of various compounds of formula (I).

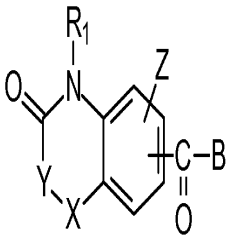
Four hours after administration of an aromatase inhibitor, the rats were sacrificed. Their uteruses were removed, cleared of adhering fat and conjunctive tissue, next the uteruses were weighed (wet weight). The dry weight of the uteruses was determined the following day after a step of drying for one night at 80 °C.

The detailed results of the activity *in vitro* and *in vivo* of various aromatase inhibitors of formula (I) according to the invention are presented in table V, in the present description.

The results show that the compounds of formula (I) according to the invention induce a reduction of uterine hypertrophy induced by androstenedione which is dependent on the dose of compound of formula (I) used, with, for certain compounds of formula (I), an almost complete inhibition of the uterine hypertrophy induced by androstenedione.

Table I-A: 6-ACYL-BENZAZINONES AND 7-ACYL-BENZOTHIAZINONES

6-Acyl-benzoxazolinones, 6-acyl-benzothiazolinones, 6-acyl-benzoxazinones, 6-acyl-benzothiazinones and 7-acyl-benzothiazinones



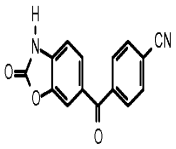
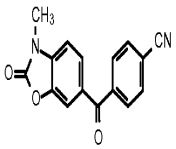
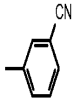
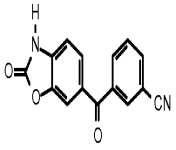
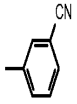
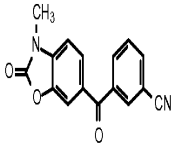
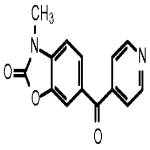
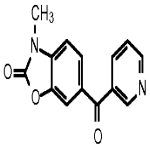
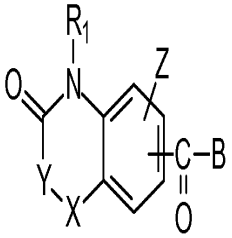
Example	R_1	X	Y	Z	B	Molecule	F°C	Method
1a	H	O	-	H			260-261	B ($AlCl_3$/DMF)
2a	CH_3	O	-	H			202-204	B
3a	H	O	-	H			260-261	B
4a	CH_3	O	-	H			200-201	B
5a	CH_3	O	-	H			181-182	B
6a	CH_3	O	-	H			163-164	B

Table I-A (continued)-BENZAZINONES AND 7-ACYL-BENZOTHIAZINONES

6-Acyl-benzoxazolinones, 6-acyl-benzothiazolinones, 6-acyl-benzoxazinones, 6-acyl-benzothiazinones and 7-acyl-benzothiazinones



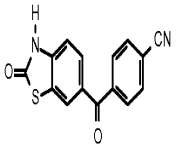
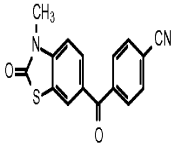
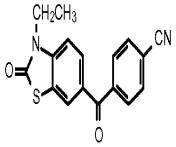
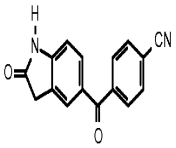
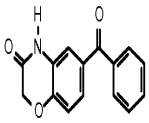
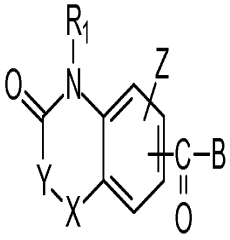
Example	R_1	X	Y	Z	B	Molecule	F°C	Method
7a	H	S	-	H			205-209	B
8a	CH_3	S	-	H			196-199	B
9a	CH_2CH_3	S	-	H			136-138	B
10a	H	CH_2	-	H			250-253	B
11a	H	O	CH_2	H			182-185	A. (PPA)

Table I-A (continued)-BENZAZINONES AND 7-ACYL-BENZOTHIAZINONES

6-Acyl-benzoxazolinones, 6-acyl-benzothiazolinones, 6-acyl-benzoxazinones, 6-acyl-benzothiazinones and 7-acyl-benzothiazinones



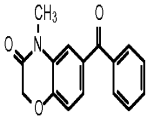
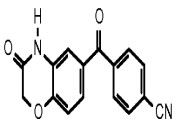
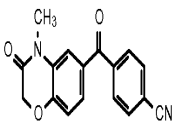
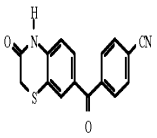
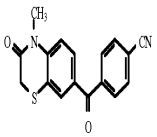
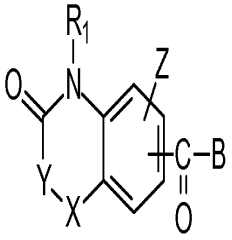
Example	R_1	X	Y	Z	B	Molecule	F°C	Method
12a	CH_3	O	CH_2	H			173-176	A.
13a	H	O	CH_2	H			280-283	B
14a	CH_3	O	CH_2	H			208-211	B
15a	H	S	CH_2	H			261-263	B
16a	CH_3	S	CH_2	H			179-180	B

Table I-A (continued)-BENZAZINONES AND 7-ACYL-BENZOTHIAZINONES

6-Acyl-benzoxazolinones, 6-acyl-benzothiazolinones, 6-acyl-benzoxazinones, 6-acyl-benzothiazinones and 7-acyl-benzothiazinones



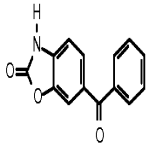
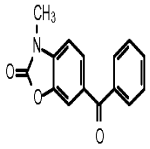
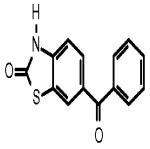
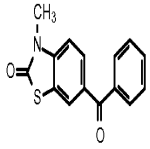
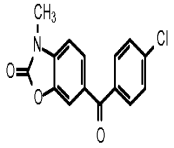
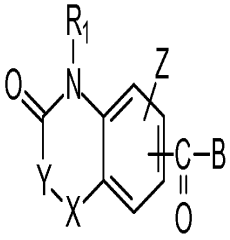
Example	R_1	X	Y	Z	B	Molecule	F°C	Method
17a	H	O	-	H			169-170	A (PPA)
18a	CH_3	O	-	H			147-148	A.
19a	H	S	-	H			216-217	A
20a	CH_3	S	-	H			148-149	A
21a	CH_3	O	-	H			190-191	A

Table I-A (continued)-BENZAZINONES AND 7-ACYL-BENZOTHIAZINONES

6-Acyl-benzoxazolinones, 6-acyl-benzothiazolinones, 6-acyl-benzoxazinones, 6-acyl-benzothiazinones and 7-acyl-benzothiazinones



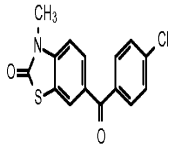
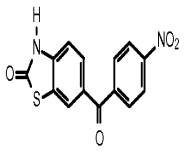
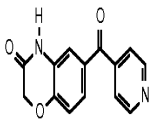
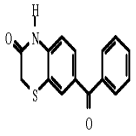
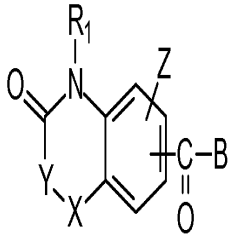
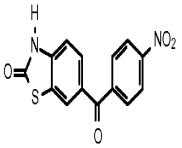
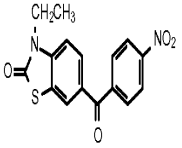
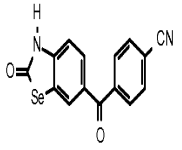
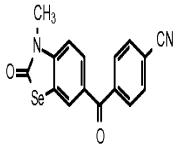
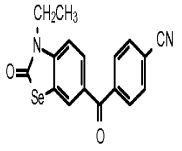
Example	R_1	X	Y	Z	B	Molecule	F°C	Method
22a	CH_3	S	-	H			176-177	A.
23a	H	S	-	H			260-265	B
24a	H	O	CH_2	H			281-282	B
25a	H	S	CH_2	H			194-196	B

Table I-B: 6-ACYL-BENZAZINONES

6-acyl-benzothiazolinones, 6-acyl- benzoselenazolinones

5



Example	R_1	X	Y	Z	B	Isomer	Molecule	F°C	Method
1	H	S	-	H		6		260-265	B ($AlCl_3$/DMF)
2	CH_2CH_3	S	-	H		6		148-152	N-alkyl
3	H	Se	-	H		6		230-232	B
4	CH_3	Se	-	H		6		205-210	B
5	CH_2CH_3	Se	-	H		6		130-135	N-alkyl

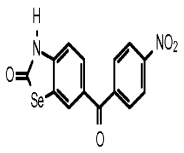
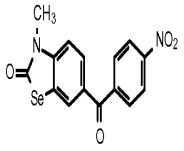
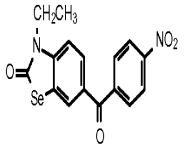
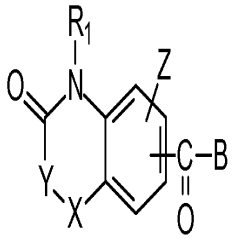
6	H	Se	-	H		6		241-245	B
7	CH_3	Se	-	H		6		151-155	N-alkyl
8	CH_2CH_3	Se	-	H		6		97-102	N-alkyl

TABLE II: 5 and 7-ACYL-BENZAZINONES

5-Acyl-benzoxazolinones, 7-acyl-benzoxazinones



5

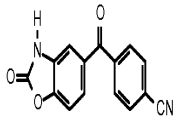
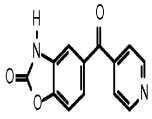
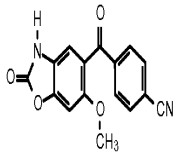
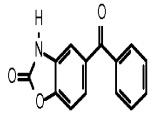
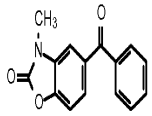
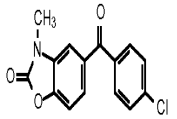
Example	R_1	X	Y	Z	B	Molecule	F°C	Preparation
26a	H	O	-	H			250-253	2
27a	H	O	-	H			307-310	2
28a	H	O	-	6-OCH_3			224-226	2
29a	H	O	-	H			153-160	2
30a	CH_3	O	-	H			152-156	2
31a	CH_3	O	-	H			163-164	2

TABLE II (continued): 5 and 7-ACYL-BENZAZINONES

5-Acyl-benzoxazolinones, 7-acyl-benzoxazinones

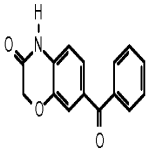
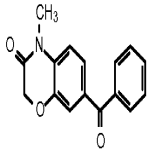
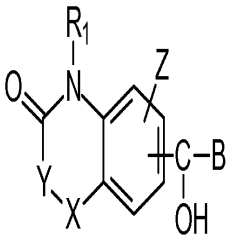
32a	H	O	CH_2	H			210-213	3
33a	CH_3	O	CH_2	H			117-119	3

Table III-A: REDUCED DERIVATIVES

Hydroxyarylmethyl benzazinones



5

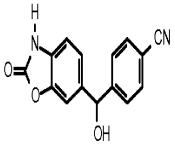
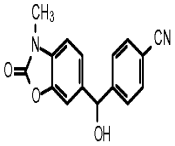
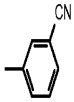
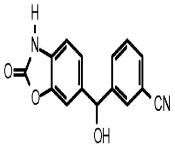
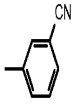
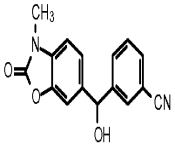
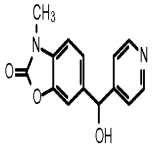
Example	R_1	X	Y	Z	B	Molecule	F°C
1b	H	O	-	H			195-197
2b	CH_3	O	-	H			145-146
3b	H	O	-	H			130-131
4b	CH_3	O	-	H			83-85
5b	CH_3	O	-	H			243-245

Table III-A (continued): REDUCED DERIVATIVES

Hydroxyarylmethyl benzazinones

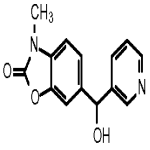
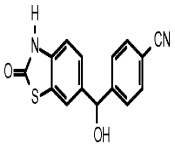
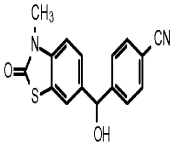
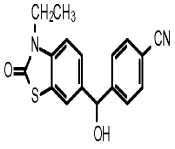
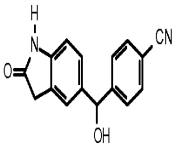
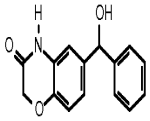
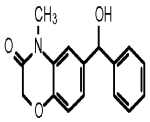
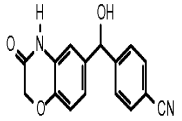
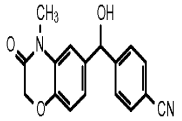
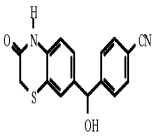
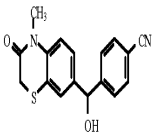
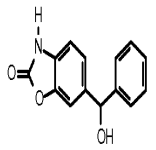
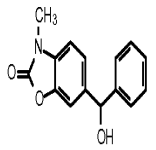
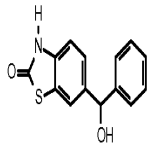
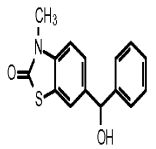
Example	R_1	X	Y	Z	B	Molecule	F°C
6b	CH_3	O	-	H			157-158
7b	H	S	-	H			202-203
8b	CH_3	S	-	H			196-197
9b	CH_2CH_3	S	-	H			146-150
10b	H	CH_2	-	H			178-180
11b	H	O	CH_2	H			180-182
12b	CH_3	O	CH_2	H			unstable

Table III-A (continued): REDUCED DERIVATIVES

Hydroxyarylmethyl benzazinones

Example	R_1	X	Y	Z	B	Molecule	F°C
13b	H	O	CH_2	H			156-160
14b	CH_3	O	CH_2	H			115-118
15b	H	S	CH_2	H			238-240
16b	CH_3	S	CH_2	H			115-118
17b	H	O	-	H			143-144
18b	CH_3	O	-	H			119-120
19b	H	S	-	H			159-160
20b	CH_3	S	-	H			127-129

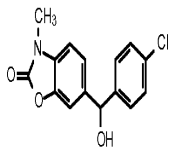
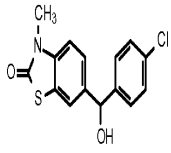
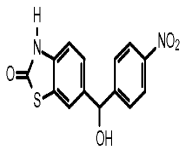
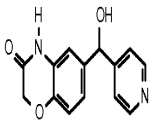
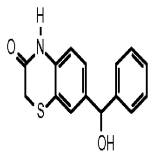
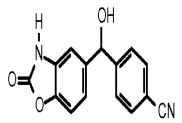
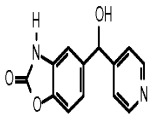
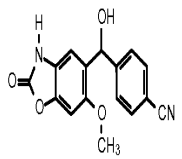
21b	CH_3	O	-	H			154-155
22b	CH_3	S	-	H			152-155
23b	H	S	-	H			208-212
24b	H	O	CH_2	H			257-260
25b	H	S	CH_2	H			173-179
26b	H	O	-	H			208-212
27b	H	O	-	H			216-220
28b	H	O	-	6-OCH_3			156-157

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Table III-A (continued): REDUCED DERIVATIVES

Hydroxyarylmethyl benzazinones

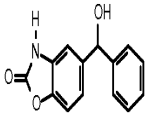
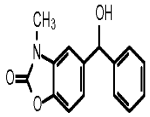
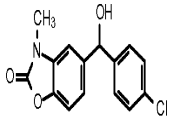
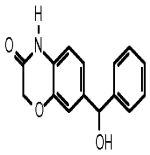
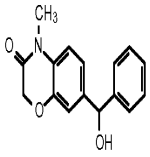
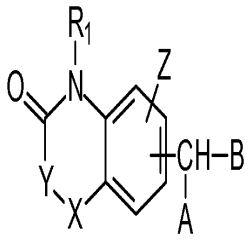
Example	R_1	X	Y	Z	B	Molecule	F°C
29b	H	O	-	H			153-154
30b	CH_3	O	-	H			127-128
31b	CH_3	O	-	H			149-153
32b	H	O	CH_2	H			132-137
33b	CH_3	O	CH_2	H			117-119

Table III-B: REDUCED DERIVATIVES

Hydroxylmethyl benzazinone



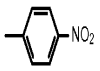
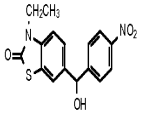
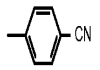
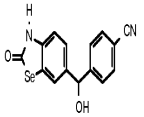
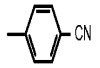
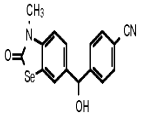
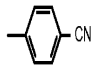
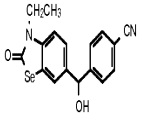
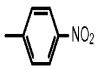
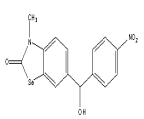
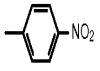
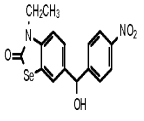
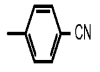
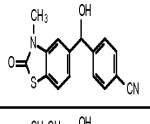
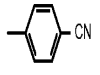
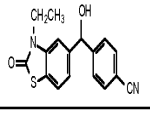
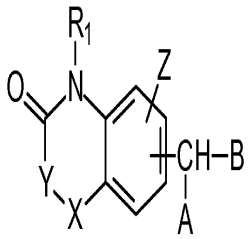
Example	R_1	X	Y	Z	B	Isomer	Molecule	F°C
1a	CH_2CH_3	S	-	H		6		160-162
2a	H	Se	-	H		6		209-213
3a	CH_3	Se	-	H		6		205-208
4a	CH_2CH_3	Se	-	H		6		132-134
5a	CH_3	Se	-	H		6		182-183
6a	CH_2CH_3	Se	-	H		6		135-137
7a	CH_3	S	-	H		5		183-186
8a	CH_2CH_3	S	-	H		5		156-158

Table IV



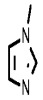
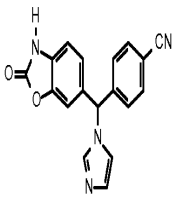
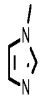
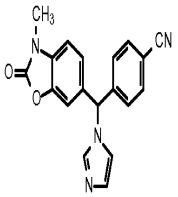
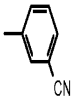
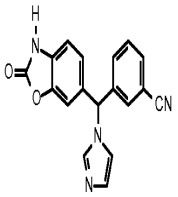
Example	Code	R_1	X	Y	Z	A	B	Molecule	F°C
1	PCH113	H	O	-	H				122-126
2	PCH27	CH_3	O	-	H				85-87
3	PCH119	H	O	-	H				113-117

Table IV (continued)

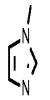
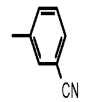
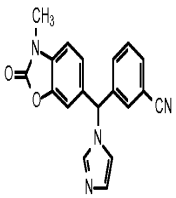
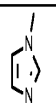
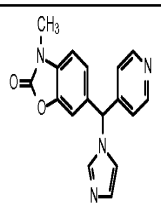
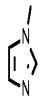
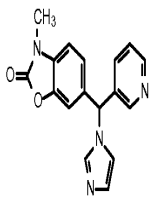
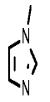
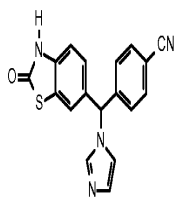
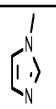
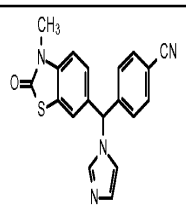
4	**PCH122**	CH_3	O	-	H				185-187
5	**PCH30**	CH_3	O	-	H				66-68
6	**PCH116**	CH_3	O	-	H				60-65
7	**PCH215**	H	S	-	H				214-216
8	**PCH165**	CH_3	S	-	H				105-108

Table IV (continued)

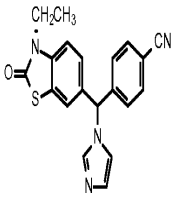
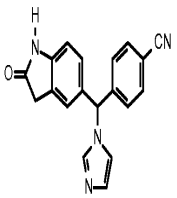
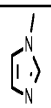
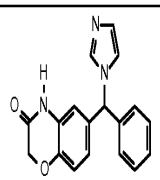
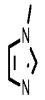
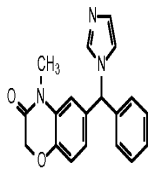
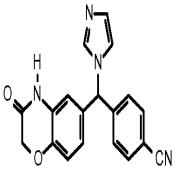
9	**PCH241**	CH_2CH_3	S	-	H				95-98
10	**PCH234**	H	CH_2	-	H				200-209
11	**PCH218**	H	O	CH_2	H				139-143
12	**PCH213**	CH_3	O	CH_2	H				123-125
13	**PCH225**	H	O	CH_2	H				135-140

Table IV (continued)

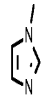
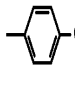
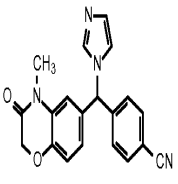
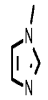
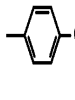
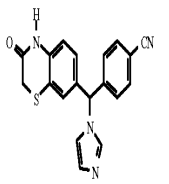
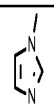
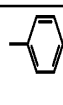
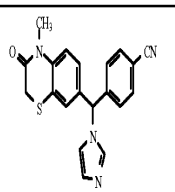
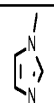
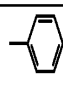
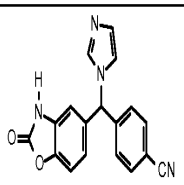
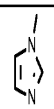
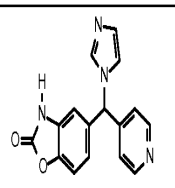
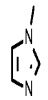
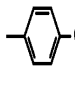
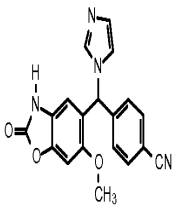
14	**PCH222**	CH_3	O	CH_2	H				80-87
15	**PCH229**	H	S	CH_2	H				150-155
16	**PCH240**	CH_3	S	CH_2	H				74-80
17	**PCH128**	H	O	-	H				128-132
18	**PCH129**	H	O	-	H				75-80
19	**GCA36**	H	O	-	6-OCH_3				165-160

Table IV (continued)

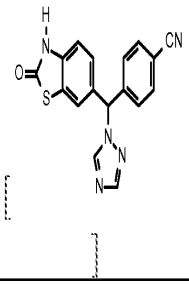
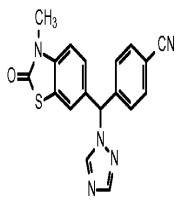
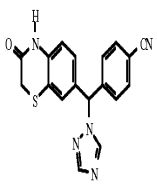
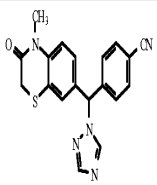
20	**PCH216**	H	S	-	H				127-130
21	**PCH158**	CH_3	S	-	H				165-168
22	**PCH230**	H	S	CH_2	H				215-218
23	**PCH231**	CH_3	S	CH_2	H				95-100

Table IV (continued)

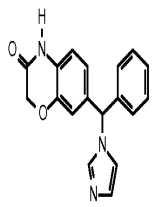
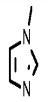
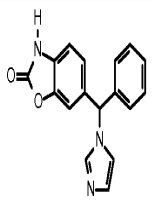
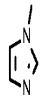
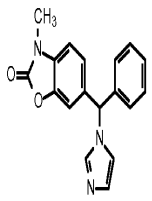
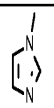
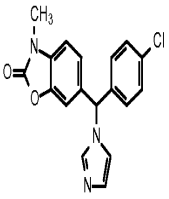
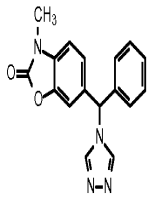
24	**PCH211**	H	O	CH_2	H				203-206
25	**PCH10**	H	O	-	H				193-195
26	**AL22**	CH_3	O	-	H				73-74
27	**PCH15**	CH_3	O	-	H				76-78
28	**PCH21**	CH_3	O	-	H				225-226

Table IV (continued)

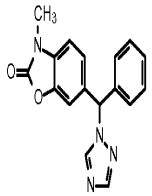
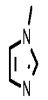
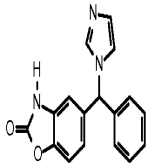
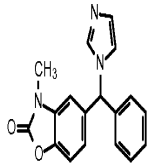
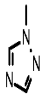
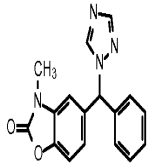
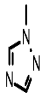
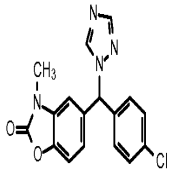
29	**PCH20**	CH_3	O	-	H				77-79
30	**PCH124**	H	O	-	H				108-111
31	**PCH31**	CH_3	O	-	H				133-135
32	**PCH183**	CH_3	O	-	H				135-138
33	**PCH160**	CH_3	O	-	H				70-74

Table IV (continued)

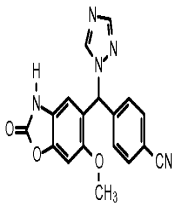
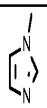
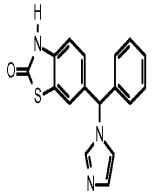
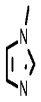
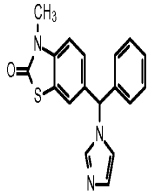
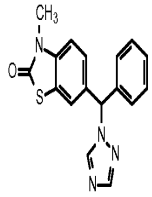
34	**GCA37**	H	O	-	6-OCH_3				125-130
35	**PCH100**	H	S	-	H				55-60
36	**PCH28**	CH_3	S	-	H				65-68
37	**PCH208**	CH_3	S	-	H				150-154

Table IV (continued)

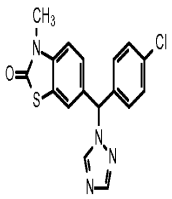
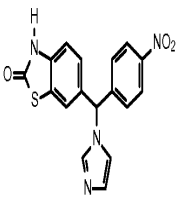
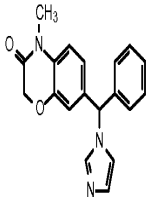
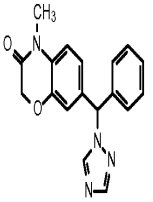
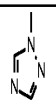
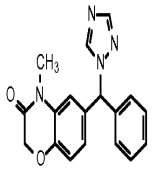
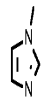
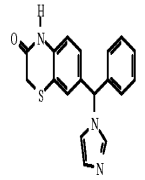
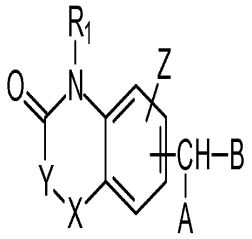
38	**PCH164**	CH_3	S	-	H				106-112
39	**PCH249**	H	S	-	H				238-241
40	**PCH19**	CH_3	O	CH_2	H				66-68
41	**PCH210**	CH_3	O	CH_2	H				160-164
42	**PCH214**	CH_3	O	CH_2	H				140-150
43	**PCH227**	H	S	CH_2	H				187-189

Table IV (continued)



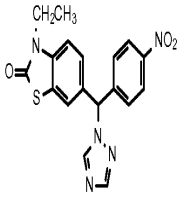
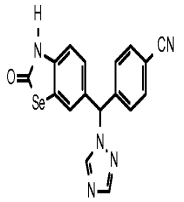
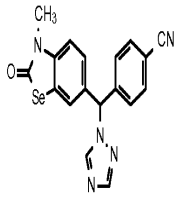
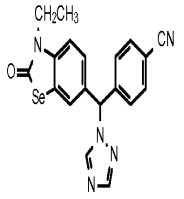
Example	Code	R_1	X	Y	Z	A	B	Isomer	Molecule	F°C
44	**PCH 243**	CH_2CH_3	S	-	H			6		79-83
45	**PCH 302**	H	Se	-	H			6		223-226
46	**PCH 300**	CH_3	Se	-	H			6		154-158
47	**PCH 303**	CH_2CH_3	Se	-	H			6		95-98

Table IV (continued)

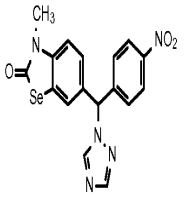
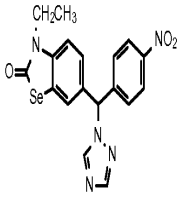
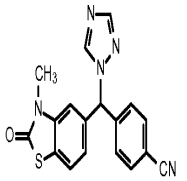
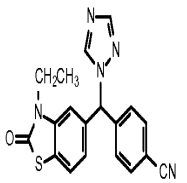
48	**PCH 304**	CH_3	Se	-	H			6		190-195
49	**PCH 305**	CH_2CH_3	Se	-	H			6		79-82
50	**PCH 163**	CH_3	S	-	H			5		122-125
51	**PCH 246**	CH_2CH_3	S	-	H			5		125-127

TABLE V

Results of tests in vitro and in vivo of compounds of formula (I) according to the invention

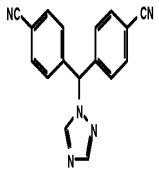
Code	Compound	*Activity In vitro* IC_{50} (nM)	% inhibition to doses (μg/Kg)
Letrozole		4.23	66% (1) 57, 59% (1) 74% (3) 91, 86% (5) 90% (10) 94, 89% (10)
(s)-Fadrozole		61 (h) 260 (e)	

TABLE V (continued)

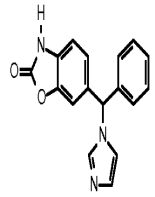
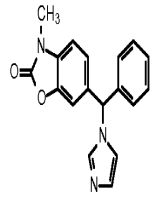
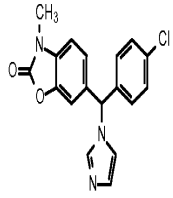
BENZOXAZOLINONIC DERIVATIVES			
Benzoxazolinonic derivatives substituted in position 6			
Code	**Compound**	***Activiy In vitro* IC_{50} (nM)**	**% inhibition to doses**
PCH10		84.63 (h) 103.3 (e)	
AL22		320 (h) 340 (e)	
PCH15		>2000 (h) nd (e)	

TABLE V (continued)

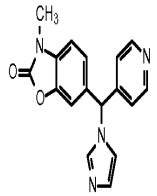
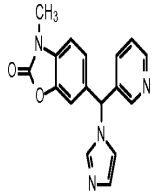
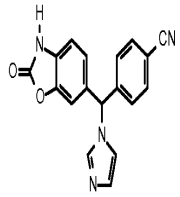
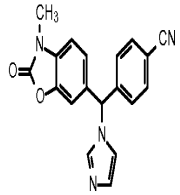
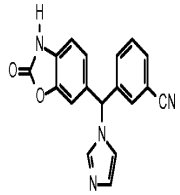
PCH30		38.0 (h) 47.7 (e)	
PCH116		33.7 (h) 34.6 (e)	
PCH113		13.25 (h) 14.6 (e)	19% (10) 50% (100) 94% (1000)
PCH27		46.2 (h) 72 (e)	
PCH119		25.05 (h) 27.7 (e)	

TABLE V (continued)

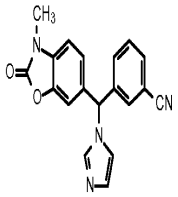
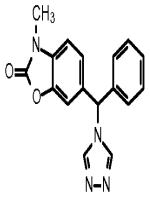
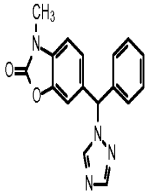
PCH122		18.63 (h) 23.25 (e)	39% (10) 58% (100) 92% (1000)
PCH21		>3000 (h) nd (e)	
PCH20		>3000 (h) nd (e)	

TABLE V (continued)

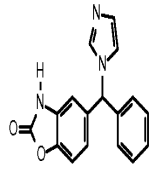
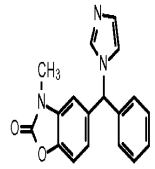
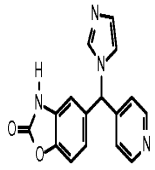
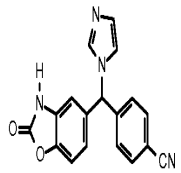
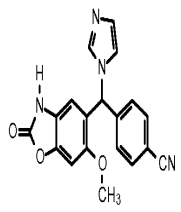
Benzoxazolinonic derivatives substituted at position 5			
Code	**Compound**	***Activiy In vitro* IC_{50} (nM)**	**% inhibition to doses (µg/kg)**
PCH124		14.95 (h) 14.1 (e)	34% (10) 71% (100) 92% (1000)
PCH31		46.6 (h) 50.1 (e)	
PCH129		26.8	
PCH128		5.83	29% (1) 29% (10) 53% (100)
GCA36		19.9	

TABLE V (continued)

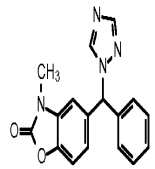
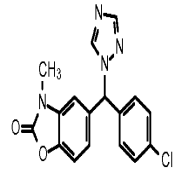
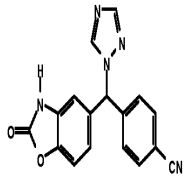
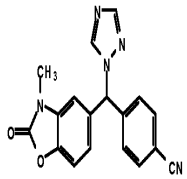
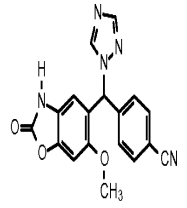
PCH183		1813	
PCH160		18.7	
PCH195		17.1	
PCH196		24.9	
GCA37		328	

TABLE V (continued)

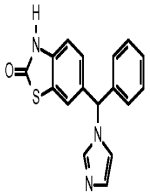
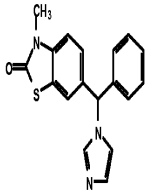
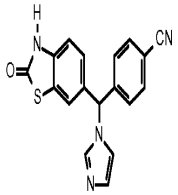
Benzothiazolinonic derivatives			
Benzothiazolinonic derivatives substituted in position 6			
Code	**Compound**	***ActivityIn vitro* IC_{50} (nM)**	**% inhibition to doses(μg/Kg)**
PCH100		33.65 (h) 34.0 (e)	
(+/-) PCH28		12.1 (h) 23.4 (e)	13% (10) 25% (100) 75% (1000)
(E1) PCH28		24.35 (h) 24.9 (e)	
(E2) PCH28		26.43 (h) 22.6 (e)	
PCH215		4.04	0% (1) 56% (10) 90% (100)

TABLE (V) continued

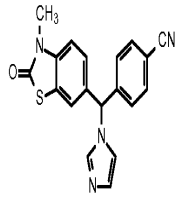
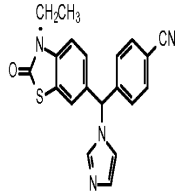
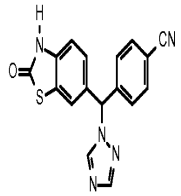
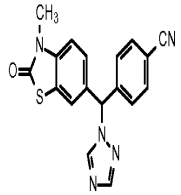
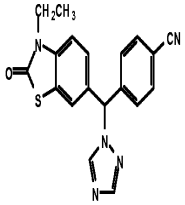
PCH165 (+/-)CD4		4.54	22% (1) 23% (10) 66% (100)
PCH165 (+)CD4		8.81	
PCH165 (-)CD4		4.94	
PCH241		4.29	18% (1) 37% (3) 16% (10)
PCH216		7.51	21% (1) 32% (10) 76% (100)
PCH158 (PCH190)		8.71	54, 60% (1) 56, 74% (10) 68, 100% (100)
PCH260		4.49	32% (1) 50% (10) 90% (100)

TABLE V (continued)

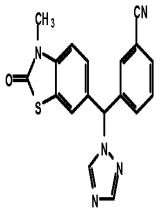
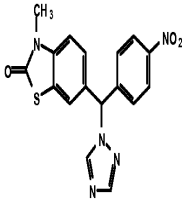
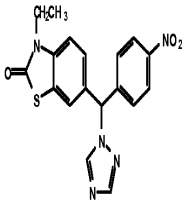
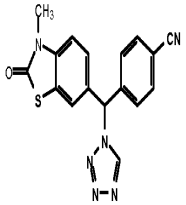
PCH258		31.7	
PCH259		3.05	31% (1) 63% (10) 88% (100)
PCH243		3.99	
PCH248		11.8	

TABLE V (continued)

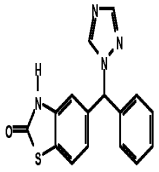
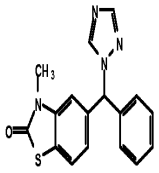
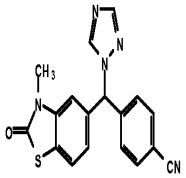
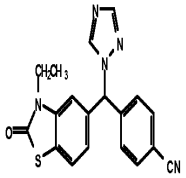
Benzothiazolinonic derivatives substituted in position 5			
Code	**Compound**	***Activiy In vitro* IC_{50} (nM)**	**% inhibition to doses(μg/Kg)**
PCH132		178	
PCH134		179	
PCH163		5.78	57% (1) 83% (10) 95% (100)
PCH246		5.51	22% (1) 45% (10) 91% (100)

TABLE V (continued)

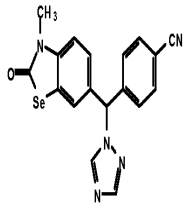
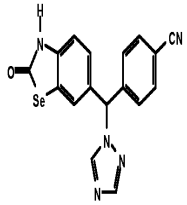
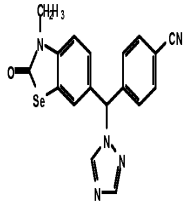
Benzoselenazolinonic derivatives			
Selenazolinonic derivatives substituted in position 6			
Code	**Compound**	***Activiy In vitro* IC_{50} (nM)**	**% inhibition to doses (μg/Kg)**
PCH300		4.64	49% (1) 86% (10) 91% (100)
PCH302		6.53	45% (1) 20% (10) 63% (100)
PCH303		3.99	38% (1) 60% (10) 71% (100)

TABLE V (continued)

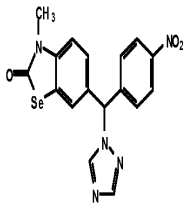
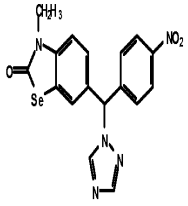
PCH304		3.64	
PCH305		3.70	

TABLE V (continued)

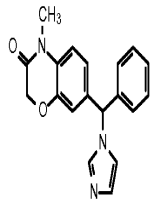
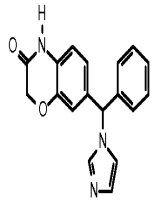
Benzoxazinonic derivatives			
Benzoxazinonic derivatives substituted at position 7			
Code	Compound	*Activiy In vitro* IC_{50} (nM)	% inhibition to doses (μg/Kg)
PCH19		52.48 (h) 59.87 (e)	
PCH211		74.4	

TABLE V (continued)

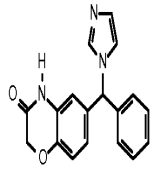
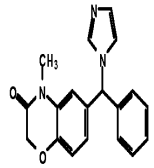
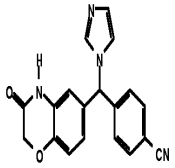
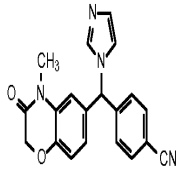
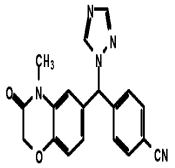
Code	Compound	*Activiy In vitro* IC_{50} (nM)	% inhibition to doses (μg/Kg)
PCH218		65.5	
PCH213		5.64	0% (1) 3% (10) 5% (100)
PCH225		9.90	
PCH222		3.44	0% (1) 22% (3) 32% (10)
PCH 223			4% (1) 22% (10) 66% (100)

TABLE V (continued)

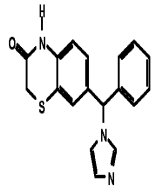
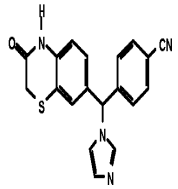
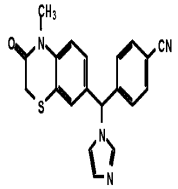
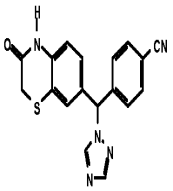
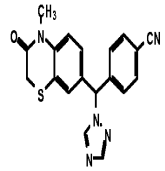
Benzothiazinonic derivatives			
Benzothiazinonic derivatives substituted in position 7			
Code	Compound	*Activiy In vitro* IC_{50} (nM)	% inhibition to doses (μg/Kg)
PCH227		55.1	
PCH229		13.8	11% (10) 42% (100) 83% (1000)
PCH240		5.38	

TABLE V (continued)

PCH230		34.8	2% (10) 22% (100) 74% (1000)
PCH231		56.6	

REFERENCES

AICHAOUI, H., LESIEUR, I., HENICHART, J.-P.
Synthesis (1990), **8**, 679-680.

AICHAOUI, H., POUPAERT, J.-H., LESIEUR, D., HENICHART, J.-P.
Tetrahedron (1991), **47**, 6649-6654.

AICHAOUI, H., LESIEUR, D., HENICHART, J.-P.
Journal of Heterocyclic Chemistry (1992), **29**: 171-175.

BERGER, P.-J.; NEGUS, N.-C.; SANDERS, E.-H.; GARDNER, P.-D.
Science (1981), **214**:69-70.

BONTE, J.-P. ; LESIEUR D. ; LESPAGNOL, C. ; CAZIN, J.-C.
European Journal of Medicinal Chemistry (1974), **9**: 491-496.

BRODIE, A.
Trends in Endocrinology and Metabolism (2002), **13**: 61-65.

BUTTERSTEIN, G.-M.; SCHADLER, M.-H.
Biology of Reproduction (1988), **39**:465-471.

KUIJPERS, A.-L.; VAN PELT, J.-P.; BERGERS, M.; BOEGHEIM, P.-J.;DEN BAKKER, J.-E.;SIEGENTHALER, G.; VAN DE KERKHOF, P.-C.;SCHALKWIJK, J.
The British Journal of Dermatology (1998), **139**: 380-389.

MOSMANN, T.
Journal of Immunology Methods (1983), **65**, 5-63.

MOUSSAVI, Z.; LESIEUR, D.; LESPAGNOL, C.; SAUZIERES, J. ; OLIVIER, P.
European Journal of Medicinal Chemistry (1989), **24**, 55-58.

PURBA, H.-S., Bhatnagar, A.-S.
Journal of Enzyme Inhibition (1990), **4**, 169-178.

SCHADLER, M. H.; BUTTERSTEIN, G. M.; FAULKNER, B. J.; RICE, S. C.; WEISINGER, L.A.

Biology of Reproduction (1988), **38**:817-820.

SERALINI, G. E.; MOSLEMI, S.

Molecular and Cellular Endocrinology (2001), **178**: 117-131.

SASTRY, C. V. ; REDDY, RAO, K. ; SRINIVASA, RASTOGI, K.; JAIN, M. L.

Indian Journal Chemistry Section B (1988) **27**; 871-873.

YOUS, S. ; POUPAERT, J. H. ; LESIEUR, I. ; DEPREUX, P. ; LESIEUR, D.

Journal of Organic Chemistry (1994), **59 :**1574-1576.